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(71) Applicant (for all designated States except US): **ALNY-LAM PHARMACEUTICALS** [US/US]; 790 Memorial Drive., Suite 202, Cambridge, MA 02139 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MANOHARAN, Muthiah** [US/US]; 25 Circle Drive, Weston, MA 02493 (US). **BUMCROT, David** [US/US]; 30 Leicester Road, Belmont, MA 02478 (US).

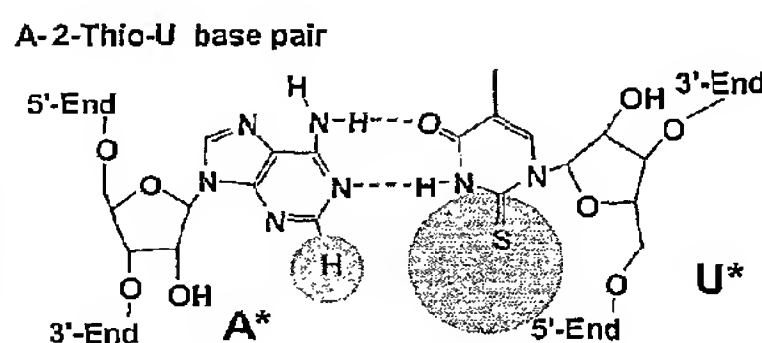
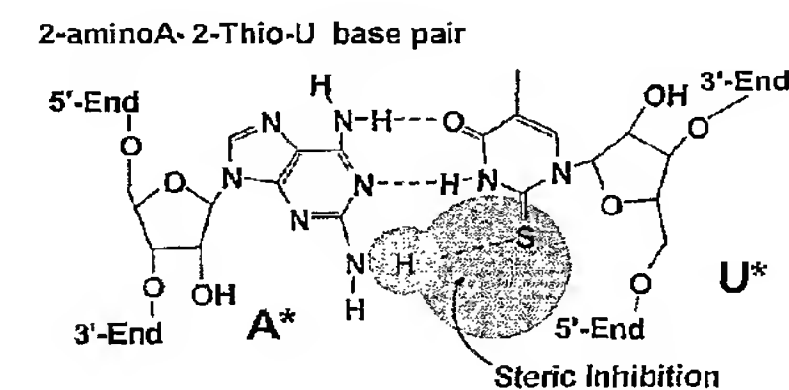
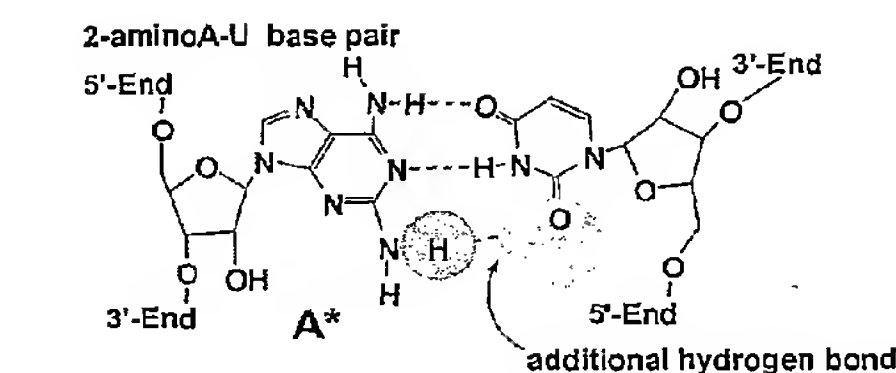
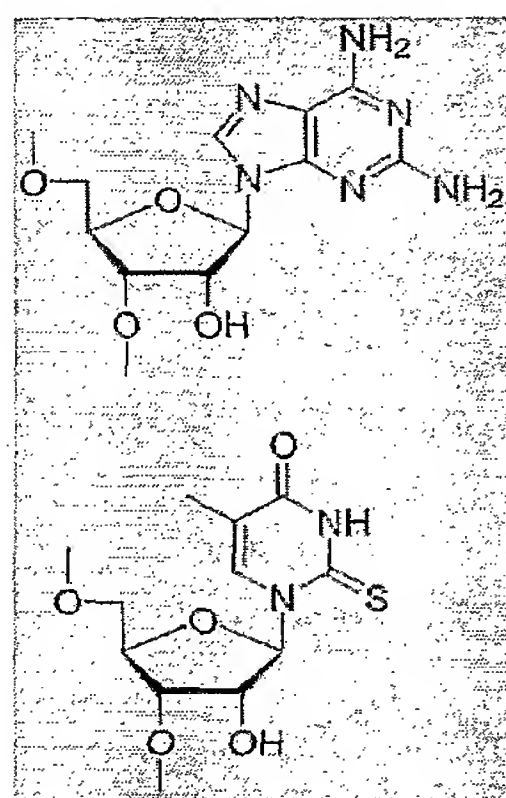
(74) Agent: **MYERS, Louis**; Fish & Richardson P.C., 225 Franklin Street, Boston, MA 02110-2804 (US).

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(54) Title: THERAPEUTIC COMPOSITIONS



(57) Abstract: Therapeutic sRNA agents and methods of making and using are enclosed.



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## THERAPEUTIC COMPOSITIONS

### RELATED APPLICATIONS

The present application claims the benefit of Application No. 60/452,682, filed  
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No. 60/510,318, filed October 10, 2003. The contents of these provisional applications are  
hereby incorporated by reference in their entirety.

15

### TECHNICAL FIELD

The invention relates to RNAi and related methods, *e.g.*, methods of making and  
using iRNA agents.

### BACKGROUND

20 RNA interference or "RNAi" is a term initially coined by Fire and co-workers to  
describe the observation that double-stranded RNA (dsRNA) can block gene expression  
when it is introduced into worms (Fire *et al.* (1998) *Nature* 391, 806-811). Short dsRNA  
directs gene-specific, post-transcriptional silencing in many organisms, including vertebrates,  
and has provided a new tool for studying gene function. RNAi may involve mRNA  
25 degradation.

## SUMMARY

A number of advances related to the application of RNAi to the treatment of subjects are disclosed herein. For example, the invention features iRNA agents targeted to specific genes; palindromic iRNA agents; iRNA agents having non canonical monomer pairings; iRNA agents having particular structures or architectures e.g., the Z-X-Y or asymmetrical iRNA agents described herein; drug delivery conjugates for the delivery of iRNA agents; amphipathic substances for the delivery of iRNA agents, as well as iRNA agents having chemical modifications for optimizing a property of the iRNA agent. The invention features each of these advances broadly as well as in combinations. For example, an iRNA agent targeted to a specific gene can also include one or more of a palindrome, non canonical, Z-X-Y, or asymmetric structure. Other nonlimiting examples of combinations include an asymmetric structure combined with a chemical modification, or formulations or methods or routes of delivery combined with, e.g., chemical modifications or architectures described herein. The iRNA agents of the invention can include any one of these advances, or pairwise or higher order combinations of the separate advances.

In one aspect, the invention features iRNA agents that can target more than one RNA region, and methods of using and making the iRNA agents.

In another aspect, an iRNA agent includes a first and second sequence that are sufficiently complementary to each other to hybridize. The first sequence can be complementary to a first target RNA region and the second sequence can be complementary to a second target RNA region.

In one embodiment, the first and second sequences of the iRNA agent are on different RNA strands, and the mismatch between the first and second sequences is less than 50%, 40%, 30%, 20%, 10%, 5%, or 1%.

In another embodiment, the first and second sequences of the iRNA agent are on the same RNA strand, and in a related embodiment more than 50%, 60%, 70%, 80%, 90%, 95%, or 1% of the iRNA agent is in bimolecular form.

In another embodiment, the first and second sequences of the iRNA agent are fully complementary to each other.

In one embodiment, the first target RNA region is encoded by a first gene and the second target RNA region is encoded by a second gene, and in another embodiment, the first

and second target RNA regions are different regions of an RNA from a single gene. In another embodiment, the first and second sequences differ by at least 1 and no more than 6 nucleotides.

5 In certain embodiments, the first and second target RNA regions are on transcripts encoded by first and second sequence variants, e.g., first and second alleles, of a gene. The sequence variants can be mutations, or polymorphisms, for example.

In certain embodiments, the first target RNA region includes a nucleotide substitution, insertion, or deletion relative to the second target RNA region.

10 In other embodiments, the second target RNA region is a mutant or variant of the first target RNA region.

In certain embodiments, the first and second target RNA regions comprise viral, e.g., HCV, or human RNA regions. The first and second target RNA regions can also be on variant transcripts of an oncogene or include different mutations of a tumor suppressor gene transcript. In one embodiment, the oncogene, or tumor suppressor gene is expressed in the  
15 liver. In addition, the first and second target RNA regions correspond to hot-spots for genetic variation.

In another aspect, the invention features a mixture of varied iRNA agent molecules, including one iRNA agent that includes a first sequence and a second sequence sufficiently complementary to each other to hybridize, and where the first sequence is complementary to  
20 a first target RNA region and the second sequence is complementary to a second target RNA region. The mixture also includes at least one additional iRNA agent variety that includes a third sequence and a fourth sequence sufficiently complementary to each other to hybridize, and where the third sequence is complementary to a third target RNA region and the fourth sequence is complementary to a fourth target RNA region. In addition, the first or second  
25 sequence is sufficiently complementary to the third or fourth sequence to be capable of hybridizing to each other. In one embodiment, at least one, two, three or all four of the target RNA regions are expressed in the liver. Exemplary RNAs are transcribed from the apoB-100 gene, glucose-6-phosphatase gene, beta catenin gene, or an HCV gene.

30 In certain embodiments, the first and second sequences are on the same or different RNA strands, and the third and fourth sequences are on same or different RNA strands.

In one embodiment, the mixture further includes a third iRNA agent that is composed of the first or second sequence and the third or fourth sequence.

In one embodiment, the first sequence is identical to at least one of the second, third and fourth sequences, and in another embodiment, the first region differs by at least 1 but no  
5 more than 6 nucleotides from at least one of the second, third and fourth regions.

In certain embodiments, the first target RNA region comprises a nucleotide substitution, insertion, or deletion relative to the second, third or fourth target RNA region.

The target RNA regions can be variant sequences of a viral or human RNA, and in certain embodiments, at least two of the target RNA regions can be on variant transcripts of  
10 an oncogene or tumor suppressor gene. In one embodiment, the oncogene or tumor suppressor gene is expressed in the liver.

In certain embodiments, at least two of the target RNA regions correspond to hot-spots for genetic variation.

In one embodiment, the iRNA agents of the invention are formulated for  
15 pharmaceutical use. In one aspect, the invention provides a container (*e.g.*, a vial, syringe, nebulizer, etc) to hold the iRNA agents described herein.

Another aspect of the invention features a method of making an iRNA agent. The method includes constructing an iRNA agent that has a first sequence complementary to a first target RNA region, and a second sequence complementary to a second target RNA  
20 region. The first and second target RNA regions have been identified as being sufficiently complementary to each other to be capable of hybridizing. In one embodiment, the first and second target RNA regions are on transcripts expressed in the liver.

In certain embodiments, the first and second target RNA regions can correspond to two different regions encoded by one gene, or to regions encoded by two different genes.

25 Another aspect of the invention features a method of making an iRNA agent composition. The method includes obtaining or providing information about a region of an RNA of a target gene (*e.g.*, a viral or human gene, or an oncogene or tumor suppressor, *e.g.*, p53), where the region has high variability or mutational frequency (*e.g.*, in humans). In addition, information about a plurality of RNA targets within the region is obtained or  
30 provided, where each RNA target corresponds to a different variant or mutant of the gene (*e.g.*, a region including the codon encoding p53 248Q and/or p53 249S). The iRNA agent is

constructed such that a first sequence is complementary to a first of the plurality of variant RNA targets (*e.g.*, encoding 249Q) and a second sequence is complementary to a second of the plurality of variant RNA targets (*e.g.*, encoding 249S). The first and second sequences are sufficiently complementary to hybridize. In certain embodiments, the target gene can be  
5 a viral or human gene expressed in the liver.

In one embodiment, sequence analysis, *e.g.*, to identify common mutants in the target gene, is used to identify a region of the target gene that has high variability or mutational frequency. For example, sequence analysis can be used to identify regions of apoB-100 or beta catenin that have high variability or mutational frequency. In another embodiment, the  
10 region of the target gene having high variability or mutational frequency is identified by obtaining or providing genotype information about the target gene from a population. In another embodiment, the genotype information can be from a population suffering from a liver disorder, such as hepatocellular carcinoma or hepatoblastoma.

Another aspect of the invention features a method of modulating expression, *e.g.*,  
15 downregulating or silencing, a target gene, by providing an iRNA agent that has a first sequence and a second sequence sufficiently complementary to each other to hybridize. In addition, the first sequence is complementary to a first target RNA region and the second sequence is complementary to a second target RNA region.

In one embodiment, the iRNA agent is administered to a subject, *e.g.*, a human.

20 In another embodiment, the first and second sequences are between 15 and 30 nucleotides in length.

In one embodiment, the method of modulating expression of the target gene further includes providing a second iRNA agent that has a third sequence complementary to a third target RNA region. The third sequence can be sufficiently complementary to the first or  
25 second sequence to be capable of hybridizing to either the first or second sequence.

Another aspect of the invention features a method of modulating expression, *e.g.*, downregulating or silencing, a plurality of target RNAs, each of the plurality of target RNAs corresponding to a different target gene. The method includes providing an iRNA agent selected by identifying a first region in a first target RNA of the plurality and a second region  
30 in a second target RNA of the plurality, where the first and second regions are sufficiently complementary to each other to be capable of hybridizing.



In another aspect of the invention, an iRNA agent molecule includes a first sequence complementary to a first variant RNA target region and a second sequence complementary to a second variant RNA target region, and the first and second variant RNA target regions correspond to first and second variants or mutants of a target gene. In certain embodiments, the target gene is an apoB-100, beta catenin, or glucose-6 phosphatase gene.

In one embodiment, the target gene is a viral gene (*e.g.*, an HCV gene), tumor suppressor or oncogene.

In another embodiment, the first and second variant target RNA regions include allelic variants of the target gene.

In another embodiment, the first and second variant RNA target regions comprise mutations (*e.g.*, point mutations) or polymorphisms of the target gene.

In one embodiment, the first and second variant RNA target regions correspond to hot-spots for genetic variation.

Another aspect of the invention features a plurality (*e.g.*, a panel or bank) of iRNA agents. Each of the iRNA agents of the plurality includes a first sequence complementary to a first variant target RNA region and a second sequence complementary to a second variant target RNA region, where the first and second variant target RNA regions correspond to first and second variants of a target gene. In certain embodiments, the variants are allelic variants of the target gene.

Another aspect of the invention provides a method of identifying an iRNA agent for treating a subject. The method includes providing or obtaining information, *e.g.*, a genotype, about a target gene, providing or obtaining information about a plurality (*e.g.*, panel or bank) of iRNA agents, comparing the information about the target gene to information about the plurality of iRNA agents, and selecting one or more of the plurality of iRNA agents for treating the subject. Each of the plurality of iRNA agents includes a first sequence complementary to a first variant target RNA region and a second sequence complementary to a second variant target RNA region, and the first and second variant target RNA regions correspond to first and second variants of the target gene. The target gene can be an endogenous gene of the subject or a viral gene. The information about the plurality of iRNA agents can be the sequence of the first or second sequence of one or more of the plurality.



In certain embodiments, at least one of the selected iRNA agents includes a sequence capable of hybridizing to an RNA region corresponding to the target gene, and at least one of the selected iRNA agents comprises a sequence capable of hybridizing to an RNA region corresponding to a variant or mutant of the target gene.

5 In one aspect, the invention relates to compositions and methods for silencing genes expressed in the liver, e.g., to treat disorders of or related to the liver. An iRNA agent composition of the invention can be one which has been modified to alter distribution in favor of the liver.

10 In another aspect, the invention relates to iRNA agents that can target more than one RNA region, and methods of using and making the iRNA agents. In one embodiment, the RNA is from a gene that is active in the liver, e.g., apoB-100, glucose-6-phosphatase, beta-catenin, or Hepatitis C virus (HCV).

15 In another aspect, an iRNA agent includes a first and second sequence that are sufficiently complementary to each other to hybridize. The first sequence can be complementary to a first target RNA region and the second sequence can be complementary to a second target RNA region. For example, the first sequence can be complementary to a first target apoB-100 RNA region and the second sequence can be complementary to a second target apoB-100 RNA region.

20 In one embodiment, the first target RNA region is encoded by a first gene, e.g., a gene expressed in the liver, and the second target RNA region is encoded by a second gene, e.g., a second gene expressed in the liver. In another embodiment, the first and second target RNA regions are different regions of an RNA from a single gene, e.g., a single gene that is at least expressed in the liver. In another embodiment, the first and second sequences differ by at least one and no more than six nucleotides.

25 In another embodiment, sequence analysis, e.g., to identify common mutants in the target gene, is used to identify a region of the target gene that has high variability or mutational frequency. For example, sequence analysis can be used to identify regions of apoB-100 or beta catenin that have high variability or mutational frequency. In another embodiment, the region of the target gene having high variability or mutational frequency is  
30 identified by obtaining or providing genotype information about the target gene from a

population. In particular, the genotype information can be from a population suffering from a liver disorder, such as hepatocellular carcinoma or hepatoblastoma.

In another aspect, the invention features a method for reducing apoB-100 levels in a subject, e.g., a mammal, such as a human. The method includes administering to a subject an  
5 iRNA agent which targets apoB-100. The iRNA agent can be one described here, and can be a dsRNA that has a sequence that is substantially identical to a sequence of the apoB-100 gene. The iRNA can be less than 30 nucleotides in length, e.g., 21-23 nucleotides. Preferably, the iRNA is 21 nucleotides in length. In one embodiment, the iRNA is 21 nucleotides in length, and the duplex region of the iRNA is 19 nucleotides. In another  
10 embodiment, the iRNA is greater than 30 nucleotides in length.

In a preferred embodiment, the subject is treated with an iRNA agent which targets one of the sequences listed in Tables 5 and 6. In a preferred embodiment it targets both sequences of a palindromic pair provided in Tables 5 and 6. The most preferred targets are listed in descending order of preferrability, in other words, the more preferred targets are  
15 listed earlier in Tables 5 and 6.

In a preferred embodiment the iRNA agent will include regions, or strands, which are complementary to a pair in Tables 5 and 6. In a preferred embodiment the iRNA agent will include regions complementary to the palindromic pairs of Tables 5 and 6 as a duplex region.

In a preferred embodiment the duplex region of the iRNA agent will target a sequence  
20 listed in Tables 5 and 6 but will not be perfectly complementary with the target sequence, e.g., it will not be complementary at at least 1 base pair. Preferably it will have no more than 1, 2, 3, 4, or 5 bases, in total, or per strand, which do not hybridize with the target sequence

In a preferred embodiment the iRNA agent includes overhangs, e.g., 3' or 5' overhangs, preferably one or more 3' overhangs. Overhangs are discussed in detail  
25 elsewhere herein but are preferably about 2 nucleotides in length. The overhangs can be complementary to the gene sequences being targeted or can be other sequence. TT is a preferred overhang sequence. The first and second iRNA agent sequences can also be joined, e.g., by additional bases to form a hairpin, or by other non-base linkers.

The iRNA agent that targets apoB-100 can be administered in an amount sufficient to  
30 reduce expression of apoB-100 mRNA. In one embodiment, the iRNA agent is administered in an amount sufficient to reduce expression of apoB-100 protein (e.g., by at least 2%, 4%,

6%, 10%, 15%, 20%). Preferably, the iRNA agent does not reduce expression of apoB-48 mRNA or protein. This can be effected, e.g., by selection of an iRNA agent which specifically targets the nucleotides subject to RNA editing in the apoB-100 transcript.

The iRNA agent that targets apoB-100 can be administered to a subject, wherein the  
5 subject is suffering from a disorder characterized by elevated or otherwise unwanted expression of apoB-100, elevated or otherwise unwanted levels of cholesterol, and/or dysregulation of lipid metabolism. The iRNA agent can be administered to an individual at risk for the disorder to delay onset of the disorder or a symptom of the disorder. These disorders include HDL/LDL cholesterol imbalance; dyslipidemias, e.g., familial combined  
10 hyperlipidemia (FCHL), acquired hyperlipidemia; hypercholesterolemia; statin-resistant hypercholesterolemia; coronary artery disease (CAD) coronary heart disease (CHD) atherosclerosis. In one embodiment, the iRNA that targets apoB-100 is administered to a subject suffering from statin-resistant hypercholesterolemia.

The apoB-100 iRNA agent can be administered in an amount sufficient to reduce  
15 levels of serum LDL-C and/or HDL-C and/or total cholesterol in a subject. For example, the iRNA is administered in an amount sufficient to decrease total cholesterol by at least 0.5%, 1%, 2.5%, 5%, 10% in the subject. In one embodiment, the iRNA agent is administered in an amount sufficient to reduce the risk of myocardial infarction the subject.

In a preferred embodiment the iRNA agent is administered repeatedly.  
20 Administration of an iRNA agent can be carried out over a range of time periods. It can be administered daily, once every few days, weekly, or monthly. The timing of administration can vary from patient to patient, depending on such factors as the severity of a patient's symptoms. For example, an effective dose of an iRNA agent can be administered to a patient once a month for an indefinite period of time, or until the patient no longer requires therapy.  
25 In addition, sustained release compositions containing an iRNA agent can be used to maintain a relatively constant dosage in the patient's blood.

In one embodiment, the iRNA agent can be targeted to the liver, and apoB expression level are decreased in the liver following administration of the apoB iRNA agent. For example, the iRNA agent can be complexed with a moiety that targets the liver, e.g., an  
30 antibody or ligand that binds a receptor on the liver.

The iRNA agent, particularly an iRNA agent that targets apoB, beta-catenin or glucose-6-phosphatase RNA, can be targeted to the liver, for example by associating, e.g., conjugating the iRNA agent to a lipophilic moiety, e.g., a lipid, cholesterol, oleyl, retinyl, or cholesteryl residue (see Table 1). Other lipophilic moieties that can be associated, e.g.,  
5 conjugated with the iRNA agent include cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine. In one embodiment, the iRNA agent can be targeted to the liver by associating,  
10 e.g., conjugating, the iRNA agent to a low-density lipoprotein (LDL), e.g., a lactosylated LDL. In another embodiment, the iRNA agent can be targeted to the liver by associating, e.g., conjugating, the iRNA agent to a polymeric carrier complex with sugar residues.

In another embodiment, the iRNA agent can be targeted to the liver by associating, e.g., conjugating, the iRNA agent to a liposome complexed with sugar residues. A targeting  
15 agent that incorporates a sugar, e.g., galactose and/or analogues thereof, is particularly useful. These agents target, in particular, the parenchymal cells of the liver (see Table 1). In a preferred embodiment, the targeting moiety includes more than one galactose moiety, preferably two or three. Preferably, the targeting moiety includes 3 galactose moieties, e.g., spaced about 15 angstroms from each other. The targeting moiety can be lactose. A lactose  
20 is a glucose coupled to a galactose. Preferably, the targeting moiety includes three lactoses. The targeting moiety can also be N-Acetyl-Galactosamine, N-Ac-Glucosamine. A mannose, or mannose-6-phosphate targeting moiety can be used for macrophage targeting.

The targeting agent can be linked directly, e.g., covalently or non covalently, to the iRNA agent, or to another delivery or formulation modality, e.g., a liposome. E.g., the iRNA  
25 agents with or without a targeting moiety can be incorporated into a delivery modality, e.g., a liposome, with or without a targeting moiety.

It is particularly preferred to use an iRNA conjugated to a lipophilic molecule to conjugate to an iRNA agent that targets apoB, beta-catenin or glucose-6-phosphatase iRNA targeting agent.

30 In one embodiment, the iRNA agent has been modified, or is associated with a delivery agent, e.g., a delivery agent described herein, e.g., a liposome, which has been



modified to alter distribution in favor of the liver. In one embodiment, the modification mediates association with a serum albumin (SA), e.g., a human serum albumin (HSA), or a fragment thereof.

The iRNA agent, particularly an iRNA agent that targets apoB, beta-catenin or glucose-6-phosphatase RNA, can be targeted to the liver, for example by associating, e.g.,  
5 conjugating the iRNA agent to an SA molecule, e.g., an HSA molecule, or a fragment thereof. In one embodiment, the iRNA agent or composition thereof has an affinity for an SA, e.g., HSA, which is sufficiently high such that its levels in the liver are at least 10, 20, 30, 50, or 100% greater in the presence of SA, e.g., HSA, or is such that addition of  
10 exogenous SA will increase delivery to the liver. These criteria can be measured, e.g., by testing distribution in a mouse in the presence or absence of exogenous mouse or human SA.

The SA, e.g., HSA, targeting agent can be linked directly, e.g., covalently or non-covalently, to the iRNA agent, or to another delivery or formulation modality, e.g., a liposome. E.g., the iRNA agents with or without a targeting moiety can be incorporated into  
15 a delivery modality, e.g., a liposome, with or without a targeting moiety.

It is particularly preferred to use an iRNA conjugated to an SA, e.g., an HSA, molecule wherein the iRNA agent is an apoB, beta-catenin or glucose-6-phosphatase iRNA targeting agent.

In another aspect, the invention features, a method for reducing glucose-6-phosphatase levels in a subject, e.g., a mammal, such as a human. The method includes  
20 administering to a subject an iRNA agent which targets glucose-6-phosphatase. The iRNA agent can be a dsRNA that has a sequence that is substantially identical to a sequence of the glucose-6-phosphatase gene.

In a preferred embodiment, the subject is treated with an iRNA agent which targets  
25 one of the sequences listed in Table 7. In a preferred embodiment it targets both sequences of a palindromic pair provided in Table 7. The most preferred targets are listed in descending order of preferrability, in other words, the more preferred targets are listed earlier in Table 7.

In a preferred embodiment the iRNA agent will include regions, or strands, which are  
30 complementary to a pair in Table 7. In a preferred embodiment the iRNA agent will include regions complementary to the palindromic pairs of Table 7 as a duplex region.

In a preferred embodiment the duplex region of the iRNA agent will target a sequence listed in Table 7 but will not be perfectly complementary with the target sequence, e.g., it will not be complementary at at least 1 base pair. Preferably it will have no more than 1, 2, 3, 4, or 5 bases, in total, or per strand, which do not hybridize with the target sequence

5 In a preferred embodiment the iRNA agent includes overhangs, e.g., 3' or 5' overhangs, preferably one or more 3' overhangs. Overhangs are discussed in detail elsewhere herein but are preferably about 2 nucleotides in length. The overhangs can be complementary to the gene sequences being targeted or can be other sequence. TT is a preferred overhang sequence. The first and second iRNA agent sequences can also be joined,  
10 e.g., by additional bases to form a hairpin, or by other non-base linkers.

Table 7 refers to sequences from human glucose-6-phosphatase. Table 8 refers to sequences from rat glucose-6-phosphatase. The sequences from table 8 can be used, e.g., in experiments with rats or cultured rat cells.

In a preferred embodiment iRNA agent can have any architecture, e.g., architecture  
15 described herein. E.g., it can be incorporated into an iRNA agent having an overhang structure, overall length, hairpin vs. two-strand structure, as described herein. In addition, monomers other than naturally occurring ribonucleotides can be used in the selected iRNA agent.

The iRNA that targets glucose-6-phosphatase can be administered in an amount  
20 sufficient to reduce expression of glucose-6-phosphatase mRNA.

The iRNA that targets glucose-6-phosphatase can be administered to a subject to inhibit hepatic glucose production, for the treatment of glucose-metabolism-related disorders, such as diabetes, e.g., type-2-diabetes mellitus. The iRNA agent can be administered to an individual at risk for the disorder to delay onset of the disorder or a symptom of the disorder.

25 In other embodiments, iRNA agents having sequence similarity to the following genes can also be used to inhibit hepatic glucose production. These other genes include "forkhead homologue in rhabdomyosarcoma (FKHR); glucagon; glucagon receptor; glycogen phosphorylase; PPAR-Gamma Coactivator (PGC-1); Fructose-1,6-bisphosphatase; glucose-6-phosphate locator; glucokinase inhibitory regulatory protein; and  
30 phosphoenolpyruvate carboxykinase (PEPCK).



In one embodiment, the iRNA agent can be targeted to the liver, and RNA expression levels of the targeted genes are decreased in the liver following administration of the iRNA agent.

The iRNA agent can be one described herein, and can be a dsRNA that has a  
5 sequence that is substantially identical to a sequence of a target gene. The iRNA can be less than 30 nucleotides in length, e.g., 21-23 nucleotides. Preferably, the iRNA is 21 nucleotides in length. In one embodiment, the iRNA is 21 nucleotides in length, and the duplex region of the iRNA is 19 nucleotides. In another embodiment, the iRNA is greater than 30 nucleotides in length

10 In another aspect, the invention features a method for reducing beta-catenin levels in a subject, e.g., a mammal, such as a human. The method includes administering to a subject an iRNA agent that targets beta-catenin. The iRNA agent can be one described herein, and can be a dsRNA that has a sequence that is substantially identical to a sequence of the beta-catenin gene. The iRNA can be less than 30 nucleotides in length, e.g., 21-23 nucleotides.  
15 Preferably, the iRNA is 21 nucleotides in length. In one embodiment, the iRNA is 21 nucleotides in length, and the duplex region of the iRNA is 19 nucleotides. In another embodiment, the iRNA is greater than 30 nucleotides in length.

In a preferred embodiment, the subject is treated with an iRNA agent which targets one of the sequences listed in Table 9. In a preferred embodiment it targets both sequences  
20 of a palindromic pair provided in Table 9. The most preferred targets are listed in descending order of preferrability, in other words, the more preferred targets are listed earlier in Table 9.

In a preferred embodiment, the subject is treated with an iRNA agent which targets one of the sequences listed in Table 9. In a preferred embodiment it targets both sequences  
25 of a palindromic pair provided in Table 9. The most preferred targets are listed in descending order of preferrability, in other words, the more preferred targets are listed earlier in Table 9.

In a preferred embodiment the iRNA agent will include regions, or strands, which are complementary to a pair in Table 9. In a preferred embodiment the iRNA agent will include  
30 regions complementary to the palindromic pairs of Table 9 as a duplex region.

In a preferred embodiment the duplex region of the iRNA agent will target a sequence listed in Table 9 but will not be perfectly complementary with the target sequence, e.g., it will not be complementary at at least 1 base pair. Preferably it will have no more than 1, 2, 3, 4, or 5 bases, in total, or per strand, which do not hybridize with the target sequence

5 In a preferred embodiment the iRNA agent includes overhangs, e.g., 3' or 5' overhangs, preferably one or more 3' overhangs. Overhangs are discussed in detail elsewhere herein but are preferably about 2 nucleotides in length. The overhangs can be complementary to the gene sequences being targeted or can be other sequence. TT is a preferred overhang sequence. The first and second iRNA agent sequences can also be joined,  
10 e.g., by additional bases to form a hairpin, or by other non-base linkers.

The iRNA agent that targets beta-catenin can be administered in an amount sufficient to reduce expression of beta-catenin mRNA. In one embodiment, the iRNA agent is administered in an amount sufficient to reduce expression of beta-catenin protein (e.g., by at least 2%, 4%, 6%, 10%, 15%, 20%).

15 The iRNA agent that targets beta-catenin can be administered to a subject, wherein the subject is suffering from a disorder characterized by unwanted cellular proliferation in the liver or of liver tissue, e.g., metastatic tissue originating from the liver. Examples include , a benign or malignant disorder, e.g., a cancer, e.g., a hepatocellular carcinoma (HCC), hepatic metastasis, or hepatoblastoma.

20 The iRNA agent can be administered to an individual at risk for the disorder to delay onset of the disorder or a symptom of the disorder

In a preferred embodiment the iRNA agent is administered repeatedly. Administration of an iRNA agent can be carried out over a range of time periods. It can be administered daily, once every few days, weekly, or monthly. The timing of administration  
25 can vary from patient to patient, depending on such factors as the severity of a patient's symptoms. For example, an effective dose of an iRNA agent can be administered to a patient once a month for an indefinite period of time, or until the patient no longer requires therapy. In addition, sustained release compositions containing an iRNA agent can be used to maintain a relatively constant dosage in the patient's blood.

30 In one embodiment, the iRNA agent can be targeted to the liver, and beta-catenin expression level are decreased in the liver following administration of the beta-catenin iRNA

agent. For example, the iRNA agent can be complexed with a moiety that targets the liver, e.g., an antibody or ligand that binds a receptor on the liver.

In another aspect, the invention provides methods to treat liver disorders, e.g., disorders characterized by unwanted cell proliferation, hematological disorders, disorders characterized by inflammation disorders, and metabolic or viral diseases or disorders of the liver. A proliferation disorder of the liver can be, for example, a benign or malignant disorder, e.g., a cancer, e.g. a hepatocellular carcinoma (HCC), hepatic metastasis, or hepatoblastoma. A hepatic hematology or inflammation disorder can be a disorder involving clotting factors, a complement-mediated inflammation or a fibrosis, for example. Metabolic diseases of the liver can include dyslipidemias, and irregularities in glucose regulation. Viral diseases of the liver can include hepatitis C or hepatitis B. In one embodiment, a liver disorder is treated by administering one or more iRNA agents that have a sequence that is substantially identical to a sequence in a gene involved in the liver disorder.

In one embodiment an iRNA agent to treat a liver disorder has a sequence which is substantially identical to a sequence of the beta-catenin or c-jun gene. In another embodiment, such as for the treatment of hepatitis C or hepatitis B, the iRNA agent can have a sequence that is substantially identical to a sequence of a gene of the hepatitis C virus or the hepatitis B virus, respectively. For example, the iRNA agent can target the 5' core region of HCV. This region lies just downstream of the ribosomal toe-print straddling the initiator methionine. Alternatively, an iRNA agent of the invention can target any one of the nonstructural proteins of HCV: NS3, 4A, 4B, 5A, or 5B. For the treatment of hepatitis B, an iRNA agent can target the protein X (HBx) gene, for example.

In a preferred embodiment, the subject is treated with an iRNA agent which targets one of the sequences listed in Table 10. In a preferred embodiment it targets both sequences of a palindromic pair provided in Table 10. The most preferred targets are listed in descending order of preferrability, in other words, the more preferred targets are listed earlier in Table 10.

In a preferred embodiment the iRNA agent will include regions, or strands, which are complementary to a pair in Table 10. In a preferred embodiment the iRNA agent will include regions complementary to the palindromic pairs of Table 10 as a duplex region.

In a preferred embodiment the duplex region of the iRNA agent will target a sequence listed in Table 10, but will not be perfectly complementary with the target sequence, e.g., it will not be complementary at at least 1 base pair. Preferably it will have no more than 1, 2, 3, 4, or 5 bases, in total, or per strand, which do not hybridize with the target sequence

5 In a preferred embodiment the iRNA agent includes overhangs, e.g., 3' or 5' overhangs, preferably one or more 3' overhangs. Overhangs are discussed in detail elsewhere herein but are preferably about 2 nucleotides in length. The overhangs can be complementary to the gene sequences being targeted or can be other sequence. TT is a preferred overhang sequence. The first and second iRNA agent sequences can also be joined,  
10 e.g., by additional bases to form a hairpin, or by other non-base linkers.

In another aspect, an iRNA agent can be administered to modulate blood clotting, e.g., to reduce the tendency to form a blood clot. In a preferred embodiment the iRNA agent targets Factor V expression, preferably in the liver. One or more iRNA agents can be used to target a wild type allele, a mutant allele, e.g., the Leiden Factor V allele, or both. Such  
15 administration can be used to treat or prevent venous thrombosis, e.g., deep vein thrombosis or pulmonary embolism, or another disorder caused by elevated or otherwise unwanted expression of Factor V, in, e.g., the liver. In one embodiment the iRNA agent can treat a subject, e.g., a human who has Factor V Leiden or other genetic trait associated with an unwanted tendency to form blood clots.

20 In a preferred embodiment administration of an iRNA agent which targets Factor V is with the administration of a second treatment, e.g., a treatment which reduces the tendency of the blood to clot, e.g., the administration of heparin or of a low molecular weight heparin.

In one embodiment, the iRNA agent that targets Factor V can be used as a prophylaxis in patients, e.g., patients with Factor V Leiden, who are placed at risk for a  
25 thrombosis, e.g., those about to undergo surgery, in particular those about to undergo high-risk surgical procedures known to be associated with formation of venous thrombosis, those about to undergo a prolonged period of relative inactivity, e.g., on a motor vehicle, train or airplane flight, e.g., a flight or other trip lasting more than three or five hours. Such a treatment can be an adjunct to the therapeutic use of low molecular weight (LMW) heparin  
30 prophylaxis.

In another embodiment, the iRNA agent that targets Factor V can be administered to patients with Factor V Leiden to treat deep vein thrombosis (DVT) or pulmonary embolism (PE). Such a treatment can be an adjunct to (or can replace) therapeutic uses of heparin or coumadin. The treatment can be administered by inhalation or generally by pulmonary routes.

In a preferred embodiment, an iRNA agent administered to treat a liver disorder is targeted to the liver. For example, the iRNA agent can be complexed with a targeting moiety, e.g., an antibody or ligand that recognizes a liver-specific receptor.

The invention also includes preparations, including substantially pure or pharmaceutically acceptable preparations of iRNA agents which silence any of the genes discussed herein and in particular for any of apoB-100, glucose-6-phosphatase, beta-catenin, factor V, or any of the HVC genes discussed herein.

The methods and compositions of the invention, e.g., the methods and compositions to treat diseases and disorders of the liver described herein, can be used with any of the iRNA agents described. In addition, the methods and compositions of the invention can be used for the treatment of any disease or disorder described herein, and for the treatment of any subject, e.g., any animal, any mammal, such as any human.

In another aspect, the invention features, a method of selecting two sequences or strands for use in an iRNA agent. The method includes:

providing a first candidate sequence and a second candidate sequence;

determining the value of a parameter which is a function of the number of palindromic pairs between the first and second sequence, wherein a palindromic pair is a nucleotide on said first sequence which, when the sequences are aligned in anti-parallel orientation, will hybridize with a nucleotide on said second sequence;

comparing the number with a predetermined reference value, and if the number has a predetermined relationship with the reference, e.g., if it is the same or greater, selecting the sequences for use in an iRNA agent. In most cases each of the two sequences will be completely complementary with a target sequence (though as described elsewhere herein that may not always be the case, there may not be perfect complementarity with one or both of the target sequences) and will have sufficient complementarity with each other to form a duplex. The parameter can be derived e.g., by directly determining the number of



palindromic pairs, e.g., by inspection or by the use of a computer program which compares or analyses sequence. The parameter can also be determined less directly, and include e.g., calculation of or measurement of the  $T_m$  or other value related to the free energy of association or dissociation of a duplex.

5 In a preferred embodiment the determination can be performed on a target sequence, e.g., a genomic sequence. In such embodiments the selected sequence is converted to its complement in the iRNA agent.

In a preferred embodiment the first and second sequences are selected from the sequence of a single target gene. In other embodiments the first sequence is selected from  
10 the sequence of a first target gene and the second sequence is selected from the target of a second target gene.

In a preferred embodiment the method includes comparing blocks of sequence, e.g., blocks which are between 15 and 25 nucleotides in length, and preferably 19, 20, or 21, and most preferably 19 nucleotides in length, to determine if they are suitable for use, e.g., if they  
15 possess sufficient palindromic pairs.

In a preferred embodiment the first and second sequences are divided into a plurality of regions, e.g., terminal regions and a middle region disposed between the terminal regions and where in the reference value, or the predetermined relationship to the reference value, is different for at least two regions. E.g., the first and second sequences, when aligned in anti-  
20 parallel orientation, are divided into terminal regions each of a selected number of base pairs, e.g., 2, 3, 4, 5, or 6, and a middle region, and the reference value for the terminal regions is higher than for the middle regions. In other words, a higher number or proportion of palindromic pairs is required in the terminal regions.

In a preferred embodiment the first and second sequences are gene sequences thus the  
25 complements of the sequences will be used in a iRNA agent.

In a preferred embodiment hybridize means a classical Watson-Crick pairing. In other embodiments hybridize can include non-Watson-Crick pairing, e.g., pairings seen in micro RNA precursors.

In a preferred embodiment the method includes the addition of nucleotides to form  
30 overhangs, e.g., 3' or 5' overhangs, preferably one or more 3' overhangs. Overhangs are discussed in detail elsewhere herein but are preferably about 2 nucleotides in length. The



overhangs can be complementary to the gene sequences being targeted or can be other sequence. TT is a preferred overhang sequence. The first and second iRNA agent sequences can also be joined, e.g., by additional bases to form a hairpin, or by other non-base linkers.

In a preferred embodiment the method is used to select all or part of a iRNA agent.

5 The selected sequences can be incorporated into an iRNA agent having any architecture, e.g., an architecture described herein. E.g., it can be incorporated into an iRNA agent having an overhang structure, overall length, hairpin vs. two-strand structure, as described herein. In addition, monomers other than naturally occurring ribonucleotides can be used in the selected iRNA agent.

10 Preferred iRNA agents of this method will target genes expressed in the liver, e.g., one of the genes disclosed herein, e.g., apo B, Beta catenin, an HVC gene, or glucose 6 phosphatase.

In another aspect, the invention features, an iRNA agent, determined, made, or selected by a method described herein.

15 The methods and compositions of the invention, e.g., the methods and iRNA compositions to treat liver-based diseases described herein, can be used with any dosage and/or formulation described herein, as well as with any route of administration described herein.

The invention also provides for the use of an iRNA agent which includes monomers which can form other than a canonical Watson-Crick pairing with another monomer, e.g., a monomer on another strand.

The use of "other than canonical Watson-Crick pairing" between monomers of a duplex can be used to control, often to promote, melting of all or part of a duplex. The iRNA agent can include a monomer at a selected or constrained position that results in a first level of stability in the iRNA agent duplex (e.g., between the two separate molecules of a double stranded iRNA agent) and a second level of stability in a duplex between a sequence of an iRNA agent and another sequence molecule, e.g., a target or off-target sequence in a subject. In some cases the second duplex has a relatively greater level of stability, e.g., in a duplex between an anti-sense sequence of an iRNA agent and a target mRNA. In this case one or more of the monomers, the position of the monomers in the iRNA agent, and the target sequence (sometimes referred to herein as the selection or constraint parameters), are

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selected such that the iRNA agent duplex is has a comparatively lower free energy of association (which while not wishing to be bound by mechanism or theory, is believed to contribute to efficacy by promoting disassociation of the duplex iRNA agent in the context of the RISC) while the duplex formed between an anti-sense targeting sequence and its target  
5 sequence, has a relatively higher free energy of association (which while not wishing to be bound by mechanism or theory, is believed to contribute to efficacy by promoting association of the anti-sense sequence and the target RNA).

In other cases the second duplex has a relatively lower level of stability, e.g., in a duplex between a sense sequence of an iRNA agent and an off-target mRNA. In this case  
10 one or more of the monomers, the position of the monomers in the iRNA agent, and an off-target sequence, are selected such that the iRNA agent duplex is has a comparatively higher free energy of association while the duplex formed between a sense targeting sequence and its off-target sequence, has a relatively lower free energy of association (which while not wishing to be bound by mechanism or theory, is believed to reduce the level of off-target  
15 silencing by contribute to efficacy by promoting disassociation of the duplex formed by the sense strand and the off-target sequence).

Thus, inherent in the structure of the iRNA agent is the property of having a first stability for the intra-iRNA agent duplex and a second stability for a duplex formed between a sequence from the iRNA agent and another RNA, e.g., a target mRNA. As discussed  
20 above, this can be accomplished by judicious selection of one or more of the monomers at a selected or constrained position, the selection of the position in the duplex to place the selected or constrained position, and selection of the sequence of a target sequence (e.g., the particular region of a target gene which is to be targeted). The iRNA agent sequences which satisfy these requirements are sometimes referred herein as constrained sequences. Exercise  
25 of the constraint or selection parameters can be, e.g., by inspection, or by computer assisted methods. Exercise of the parameters can result in selection of a target sequence and of particular monomers to give a desired result in terms of the stability, or relative stability, of a duplex.

Thus, in one aspect, the invention features, an iRNA agent which includes: a first  
30 sequence which targets a first target region and a second sequence which targets a second target region. The first and second sequences have sufficient complementarity to each other

to hybridize, e.g., under physiological conditions, e.g., under physiological conditions but not in contact with a helicase or other unwinding enzyme. In a duplex region of the iRNA agent, at a selected or constrained position, the first target region has a first monomer, and the second target region has a second monomer. The first and second monomers occupy  
5 complementary or corresponding positions. One, and preferably both monomers are selected such that the stability of the pairing of the monomers contribute to a duplex between the first and second sequence will differ from the stability of the pairing between the first or second sequence with a target sequence.

Usually, the monomers will be selected (selection of the target sequence may be  
10 required as well) such that they form a pairing in the iRNA agent duplex which has a lower free energy of dissociation, and a lower  $T_m$ , than will be possessed by the pairing of the monomer with its complementary monomer in a duplex between the iRNA agent sequence and a target RNA duplex.

The constraint placed upon the monomers can be applied at a selected site or at more  
15 than one selected site. By way of example, the constraint can be applied at more than 1, but less than 3, 4, 5, 6, or 7 sites in an iRNA agent duplex.

A constrained or selected site can be present at a number of positions in the iRNA agent duplex. E.g., a constrained or selected site can be present within 3, 4, 5, or 6 positions from either end, 3' or 5' of a duplexed sequence. A constrained or selected site can be  
20 present in the middle of the duplex region, e.g., it can be more than 3, 4, 5, or 6, positions from the end of a duplexed region.

The iRNA agent can be selected to target a broad spectrum of genes, including any of the genes described herein.

In a preferred embodiment the iRNA agent has an architecture (architecture refers to  
25 one or more of overall length, length of a duplex region, the presence, number, location, or length of overhangs, single strand versus double strand form) described herein.

E.g., the iRNA agent can be less than 30 nucleotides in length, e.g., 21-23 nucleotides. Preferably, the iRNA is 21 nucleotides in length and there is a duplex region of about 19 pairs. In one embodiment, the iRNA is 21 nucleotides in length, and the duplex  
30 region of the iRNA is 19 nucleotides. In another embodiment, the iRNA is greater than 30 nucleotides in length.

In some embodiment the duplex region of the iRNA agent will have, mismatches, in addition to the selected or constrained site or sites. Preferably it will have no more than 1, 2, 3, 4, or 5 bases, which do not form canonical Watson-Crick pairs or which do not hybridize. Overhangs are discussed in detail elsewhere herein but are preferably about 2 nucleotides in length. The overhangs can be complementary to the gene sequences being targeted or can be other sequence. TT is a preferred overhang sequence. The first and second iRNA agent sequences can also be joined, e.g., by additional bases to form a hairpin, or by other non-base linkers.

The monomers can be selected such that: first and second monomers are naturally occurring ribonucleotides, or modified ribonucleotides having naturally occurring bases, and when occupying complementary sites either do not pair and have no substantial level of H-bonding, or form a non canonical Watson-Crick pairing and form a non-canonical pattern of H bonding, which usually have a lower free energy of dissociation than seen in a canonical Watson-Crick pairing, or otherwise pair to give a free energy of association which is less than that of a preselected value or is less, e.g., than that of a canonical pairing. When one (or both) of the iRNA agent sequences duplexes with a target, the first (or second) monomer forms a canonical Watson-Crick pairing with the base in the complementary position on the target, or forms a non canonical Watson-Crick pairing having a higher free energy of dissociation and a higher  $T_m$  than seen in the pairing in the iRNA agent. The classical Watson-Crick pairings are as follows: A-T, G-C, and A-U. Non-canonical Watson-Crick pairings are known in the art and can include, U-U, G-G, G-Atrans, G-Acis, and GU.

The monomer in one or both of the sequences is selected such that, it does not pair, or forms a pair with its corresponding monomer in the other sequence which minimizes stability (e.g., the H bonding formed between the monomer at the selected site in the one sequence and its monomer at the corresponding site in the other sequence are less stable than the H bonds formed by the monomer one (or both) of the sequences with the respective target sequence. The monomer in one or both strands is also chosen to promote stability in one or both of the duplexes made by a strand and its target sequence. E.g., one or more of the monomers and the target sequences are selected such that at the selected or constrained position, there is are no H bonds formed, or a non canonical pairing is formed in the iRNA agent duplex, or otherwise they otherwise pair to give a free energy of association which is



less than that of a preselected value or is less, e.g., than that of a canonical pairing, but when one ( or both) sequences form a duplex with the respective target, the pairing at the selected or constrained site is a canonical Watson-Crick pairing.

The inclusion of such a monomers will have one or more of the following effects: it  
5 will destabilize the iRNA agent duplex, it will destabilize interactions between the sense sequence and unintended target sequences, sometimes referred to as off-target sequences, and duplex interactions between the a sequence and the intended target will not be destabilized.

By way of example:

the monomer at the selected site in the first sequence includes an A (or a modified  
10 base which pairs with T), and the monomer in at the selected position in the second sequence is chosen from a monomer which will not pair or which will form a non-canonical pairing, e.g., G. These will be useful in applications wherein the target sequence for the first sequence has a T at the selected position. In embodiments where both target duplexes are stabilized it is useful wherein the target sequence for the second strand has a monomer which  
15 will form a canonical Watson-Crick pairing with the monomer selected for the selected position in the second strand.

the monomer at the selected site in the first sequence includes U (or a modified base which pairs with A), and the monomer in at the selected position in the second sequence is chosen from a monomer which will not pair or which will form a non-canonical pairing, e.g.,  
20 U or G. These will be useful in applications wherein the target sequence for the first sequence has a T at the selected position. In embodiments where both target duplexes are stabilized it is useful wherein the target sequence for the second strand has a monomer which will form a canonical Watson-Crick pairing with the monomer selected for the selected position in the second strand.

25 The monomer at the selected site in the first sequence includes a G (or a modified base which pairs with C), and the monomer in at the selected position in the second sequence is chosen from a monomer which will not pair or which will form a non-canonical pairing, e.g., G, Acis, Atrans, or U. These will be useful in applications wherein the target sequence for the first sequence has a T at the selected position. In embodiments where both target  
30 duplexes are stabilized it is useful wherein the target sequence for the second strand has a

monomer which will form a canonical Watson-Crick pairing with the monomer selected for the selected position in the second strand.

The monomer at the selected site in the first sequence includes a C (or a modified base which pairs with G), and the monomer in at the selected position in the second sequence is chosen a monomer which will not pair or which will form a non-canonical pairing. These will be useful in applications wherein the target sequence for the first sequence has a T at the selected position. In embodiments where both target duplexes are stabilized it is useful wherein the target sequence for the second strand has a monomer which will form a canonical Watson-Crick pairing with the monomer selected for the selected position in the second strand.

In another embodiment a non-naturally occurring or modified monomer or monomers are chosen such that when a non-naturally occurring or modified monomer occupies a positions at the selected or constrained position in an iRNA agent they exhibit a first free energy of dissociation and when one (or both) of them pairs with a naturally occurring monomer, the pair exhibits a second free energy of dissociation, which is usually higher than that of the pairing of the first and second monomers. E.g., when the first and second monomers occupy complementary positions they either do not pair and have no substantial level of H-bonding, or form a weaker bond than one of them would form with a naturally occurring monomer, and reduce the stability of that duplex, but when the duplex dissociates at least one of the strands will form a duplex with a target in which the selected monomer will promote stability, e.g., the monomer will form a more stable pair with a naturally occurring monomer in the target sequence than the pairing it formed in the iRNA agent.

An example of such a pairing is 2-amino A and either of a 2-thio pyrimidine analog of U or T.

When placed in complementary positions of the iRNA agent these monomers will pair very poorly and will minimize stability. However, a duplex is formed between 2 amino A and the U of a naturally occurring target, or a duplex is between 2-thio U and the A of a naturally occurring target or 2-thio T and the A of a naturally occurring target will have a relatively higher free energy of dissociation and be more stable. This is shown in the FIG. 1.

The pair shown in FIG. 1 (the 2-amino A and the 2-s U and T) is exemplary. In another embodiment, the monomer at the selected position in the sense strand can be a



universal pairing moiety. A universal pairing agent will form some level of H bonding with more than one and preferably all other naturally occurring monomers. An example of a universal pairing moiety is a monomer which includes 3-nitro pyrrole. (Examples of other candidate universal base analogs can be found in the art, e.g., in Loakes, 2001, NAR 29: 2437-2447, hereby incorporated by reference. Examples can also be found in the section on Universal Bases below.) In these cases the monomer at the corresponding position of the anti-sense strand can be chosen for its ability to form a duplex with the target and can include, e.g., A, U, G, or C.

In another aspect, the invention features, an iRNA agent which includes: a sense sequence, which preferably does not target a sequence in a subject, and an anti-sense sequence, which targets a target gene in a subject. The sense and anti-sense sequences have sufficient complementarity to each other to hybridize hybridize, e.g., under physiological conditions, e.g., under physiological conditions but not in contact with a helicase or other unwinding enzyme. In a duplex region of the iRNA agent, at a selected or constrained position, the monomers are selected such that:

the monomer in the sense sequence is selected such that, it does not pair, or forms a pair with its corresponding monomer in the anti-sense strand which minimizes stability (e.g., the H bonding formed between the monomer at the selected site in the sense strand and its monomer at the corresponding site in the anti-sense strand are less stable than the H bonds formed by the monomer of the anti-sense sequence and its canonical Watson-Crick partner or, if the monomer in the anti-sense strand includes a modified base, the natural analog of the modified base and its canonical Watson-Crick partner);

the monomer in the corresponding position in the anti-sense strand is selected such that it maximizes the stability of a duplex it forms with the target sequence, e.g., it forms a canonical Watson-Crick paring with the monomer in the corresponding position on the target stand;

optionally, the monomer in the sense sequence is selected such that, it does not pair, or forms a pair with its corresponding monomer in the anti-sense strand which minimizes stability with an off-target sequence.

The inclusion of such a monomers will have one or more of the following effects: it will destabilize the iRNA agent duplex, it will destabilize interactions between the sense

sequence and unintended target sequences, sometimes referred to as off-target sequences, and duplex interactions between the anti-sense strand and the intended target will not be destabilized.

The constraint placed upon the monomers can be applied at a selected site or at more than one selected site. By way of example, the constraint can be applied at more than 1, but less than 3, 4, 5, 6, or 7 sites in an iRNA agent duplex.

A constrained or selected site can be present at a number of positions in the iRNA agent duplex. E.g., a constrained or selected site can be present within 3, 4, 5, or 6 positions from either end, 3' or 5' of a duplexed sequence. A constrained or selected site can be present in the middle of the duplex region, e.g., it can be more than 3, 4, 5, or 6, positions from the end of a duplexed region.

The iRNA agent can be selected to target a broad spectrum of genes, including any of the genes described herein.

In a preferred embodiment the iRNA agent has an architecture (architecture refers to one or more of overall length, length of a duplex region, the presence, number, location, or length of overhangs, sing strand versus double strand form) described herein.

E.g., the iRNA agent can be less than 30 nucleotides in length, *e.g.*, 21-23 nucleotides. Preferably, the iRNA is 21 nucleotides in length and there is a duplex region of about 19 pairs. In one embodiment, the iRNA is 21 nucleotides in length, and the duplex region of the iRNA is 19 nucleotides. In another embodiment, the iRNA is greater than 30 nucleotides in length.

In some embodiment the duplex region of the iRNA agent will have, mismatches, in addition to the selected or constrained site or sites. Preferably it will have no more than 1, 2, 3, 4, or 5 bases, which do not form canonical Watson-Crick pairs or which do not hybridize. Overhangs are discussed in detail elsewhere herein but are preferably about 2 nucleotides in length. The overhangs can be complementary to the gene sequences being targeted or can be other sequence. TT is a preferred overhang sequence. The first and second iRNA agent sequences can also be joined, e.g., by additional bases to form a hairpin, or by other non-base linkers.

One or more selection or constraint parameters can be exercised such that: monomers at the selected site in the sense and anti-sense sequences are both naturally occurring

ribonucleotides, or modified ribonucleotides having naturally occurring bases, and when occupying complementary sites in the iRNA agent duplex either do not pair and have no substantial level of H-bonding, or form a non-canonical Watson-Crick pairing and thus form a non-canonical pattern of H bonding, which generally have a lower free energy of dissociation than seen in a Watson-Crick pairing, or otherwise pair to give a free energy of association which is less than that of a preselected value or is less, e.g., than that of a canonical pairing. When one, usually the anti-sense sequence of the iRNA agent sequences forms a duplex with another sequence, generally a sequence in the subject, and generally a target sequence, the monomer forms a classic Watson-Crick pairing with the base in the complementary position on the target, or forms a non-canonical Watson-Crick pairing having a higher free energy of dissociation and a higher  $T_m$  than seen in the pairing in the iRNA agent. Optionally, when the other sequence of the iRNA agent, usually the sense sequences forms a duplex with another sequence, generally a sequence in the subject, and generally an off-target sequence, the monomer fails to form a canonical Watson-Crick pairing with the base in the complementary position on the off target sequence, e.g., it forms or forms a non-canonical Watson-Crick pairing having a lower free energy of dissociation and a lower  $T_m$ .

By way of example:

the monomer at the selected site in the anti-sense strand includes an A (or a modified base which pairs with T), the corresponding monomer in the target is a T, and the sense strand is chosen from a base which will not pair or which will form a noncanonical pair, e.g., G;

the monomer at the selected site in the anti-sense strand includes a U (or a modified base which pairs with A), the corresponding monomer in the target is an A, and the sense strand is chosen from a monomer which will not pair or which will form a non-canonical pairing, e.g., U or G;

the monomer at the selected site in the anti-sense strand includes a C (or a modified base which pairs with G), the corresponding monomer in the target is a G, and the sense strand is chosen a monomer which will not pair or which will form a non-canonical pairing, e.g., G,  $A_{cis}$ ,  $A_{trans}$ , or U; or

the monomer at the selected site in the anti-sense strand includes a G (or a modified base which pairs with C), the corresponding monomer in the target is a C, and the sense

strand is chosen from a monomer which will not pair or which will form a non-canonical pairing.

In another embodiment a non-naturally occurring or modified monomer or monomers is chosen such that when it occupies complementary a position in an iRNA agent they exhibit  
5 a first free energy of dissociation and when one (or both) of them pairs with a naturally occurring monomer, the pair exhibits a second free energy of dissociation, which is usually higher than that of the pairing of the first and second monomers. E.g., when the first and second monomers occupy complementary positions they either do not pair and have no substantial level of H-bonding, or form a weaker bond than one of them would form with a  
10 naturally occurring monomer, and reduce the stability of that duplex, but when the duplex dissociates at least one of the strands will form a duplex with a target in which the selected monomer will promote stability, e.g., the monomer will form a more stable pair with a naturally occurring monomer in the target sequence than the pairing it formed in the iRNA agent.

15 An example of such a pairing is 2-amino A and either of a 2-thio pyrimidine analog of U or T. As is discussed above, when placed in complementary positions of the iRNA agent these monomers will pair very poorly and will minimize stability. However, a duplex is formed between 2 amino A and the U of a naturally occurring target, or a duplex is formed between 2-thio U and the A of a naturally occurring target or 2-thio T and the A of a  
20 naturally occurring target will have a relatively higher free energy of dissociation and be more stable.

The monomer at the selected position in the sense strand can be a universal pairing moiety. A universal pairing agent will form some level of H bonding with more than one and preferably all other naturally occurring monomers. An examples of a universal pairing  
25 moiety is a monomer which includes 3-nitro pyrrole. Examples of other candidate universal base analogs can be found in the art, e.g., in Loakes, 2001, NAR 29: 2437-2447, hereby incorporated by reference. In these cases the monomer at the corresponding position of the anti-sense strand can be chosen for its ability to form a duplex with the target and can include, e.g., A, U, G, or C.

30 In another aspect, the invention features, an iRNA agent which includes:

a sense sequence, which preferably does not target a sequence in a subject, and an anti-sense sequence, which targets a plurality of target sequences in a subject, wherein the targets differ in sequence at only 1 or a small number, e.g., no more than 5, 4, 3 or 2 positions. The sense and anti-sense sequences have sufficient complementarity to each other to hybridize, e.g.,  
5 under physiological conditions, e.g., under physiological conditions but not in contact with a helicase or other unwinding enzyme. In the sequence of the anti-sense strand of the iRNA agent is selected such that at one, some, or all of the positions which correspond to positions that differ in sequence between the target sequences, the anti-sense strand will include a monomer which will form H-bonds with at least two different target sequences. In a  
10 preferred example the anti-sense sequence will include a universal or promiscuous monomer, e.g., a monomer which includes 5-nitro pyrrole, 2-amino A, 2-thio U or 2-thio T, or other universal base referred to herein.

In a preferred embodiment the iRNA agent targets repeated sequences (which differ at only one or a small number of positions from each other) in a single gene, a plurality of  
15 genes, or a viral genome, e.g., the HCV genome.

An embodiment is illustrated in the FIGs. 2 and 3.

In another aspect, the invention features, determining, e.g., by measurement or calculation, the stability of a pairing between monomers at a selected or constrained position in the iRNA agent duplex, and preferably determining the stability for the corresponding  
20 pairing in a duplex between a sequence from the iRNA agent and another RNA, e.g., a target sequence. The determinations can be compared. An iRNA agent thus analyzed can be used in the development of a further modified iRNA agent or can be administered to a subject. This analysis can be performed successively to refine or design optimized iRNA agents.

In another aspect, the invention features, a kit which includes one or more of the  
25 following an iRNA described herein, a sterile container in which the iRNA agent is disclosed, and instructions for use.

In another aspect, the invention features, an iRNA agent containing a constrained sequence made by a method described herein. The iRNA agent can target one or more of the genes referred to herein.

30 iRNA agents having constrained or selected sites, e.g., as described herein, can be used in any way described herein. Accordingly, they iRNA agents having constrained or



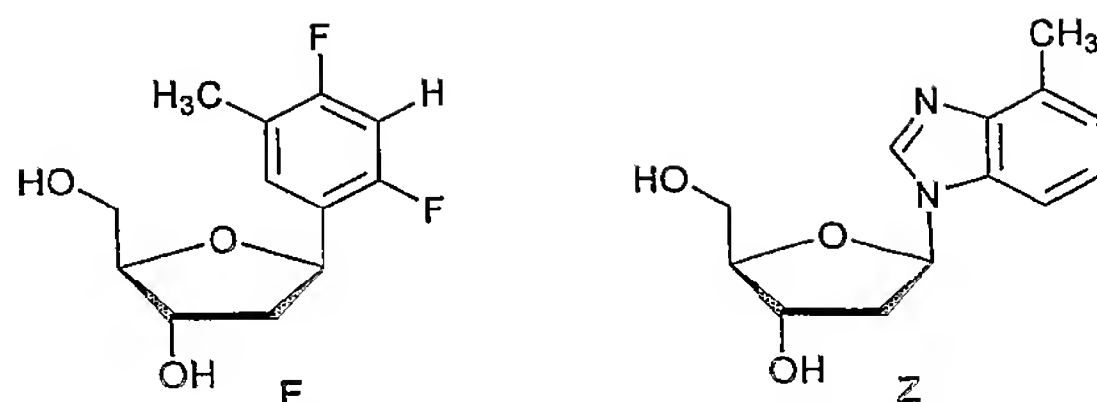
selected sites, e.g., as described herein, can be used to silence a target, e.g., in any of the methods described herein and to target any of the genes described herein or to treat any of the disorders described herein. iRNA agents having constrained or selected sites, e.g., as described herein, can be incorporated into any of the formulations or preparations, e.g., pharmaceutical or sterile preparations described herein. iRNA agents having constrained or selected sites, e.g., as described herein, can be administered by any of the routes of administration described herein.

The term "other than canonical Watson-Crick pairing" as used herein, refers to a pairing between a first monomer in a first sequence and a second monomer at the corresponding position in a second sequence of a duplex in which one or more of the following is true: (1) there is essentially no pairing between the two, e.g., there is no significant level of H bonding between the monomers or binding between the monomers does not contribute in any significant way to the stability of the duplex; (2) the monomers are a non-canonical pairing of monomers having a naturally occurring bases, i.e., they are other than A-T, A-U, or G-C, and they form monomer-monomer H bonds, although generally the H bonding pattern formed is less strong than the bonds formed by a canonical pairing; or (3) at least one of the monomers includes a non-naturally occurring bases and the H bonds formed between the monomers is, preferably formed is less strong than the bonds formed by a canonical pairing, namely one or more of A-T, A-U, G-C.

The term "off-target" as used herein, refers to a sequence other than the sequence to be silenced.

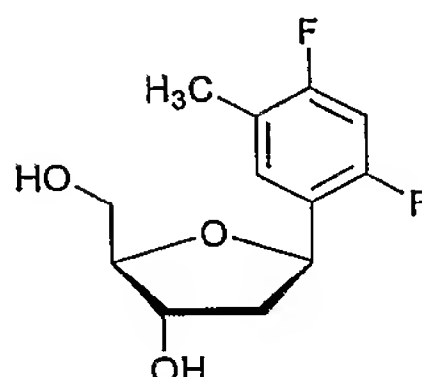
#### Universal Bases: "wild-cards" ; shape-based complementarity

Bi-stranded, multisite replication of a base pair between difluorotoluene and adenine: confirmation by 'inverse' sequencing. Liu, D.; Moran, S.; Kool, E. T. *Chem. Biol.*, **1997**, *4*, 919-926)



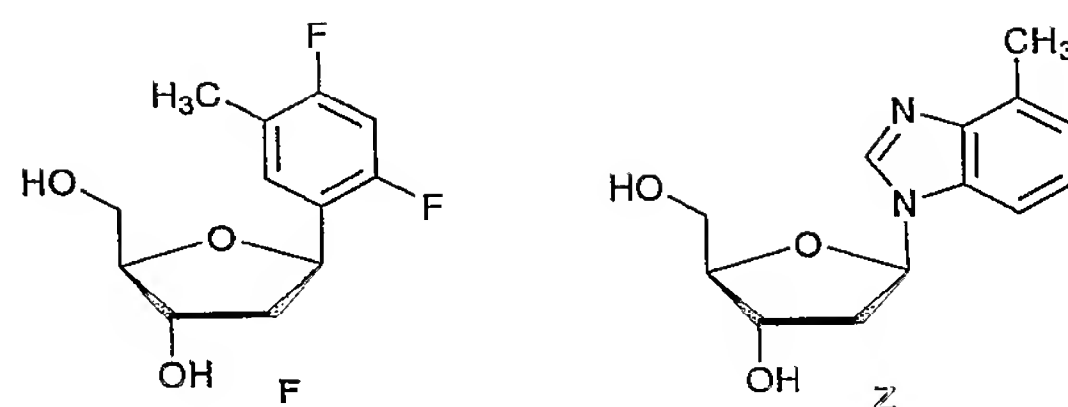
(Importance of terminal base pair hydrogen-bonding in 3'-end proofreading by the Klenow fragment of DNA polymerase I. Morales, J. C.; Kool, E. T. *Biochemistry*, **2000**, 39, 2626-2632)

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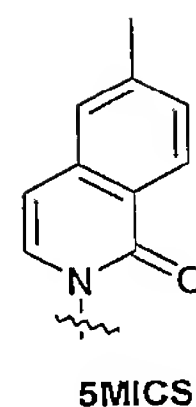
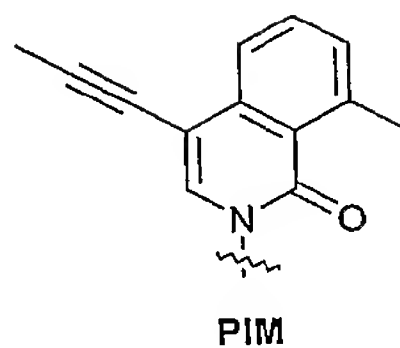
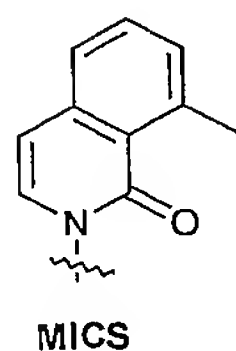
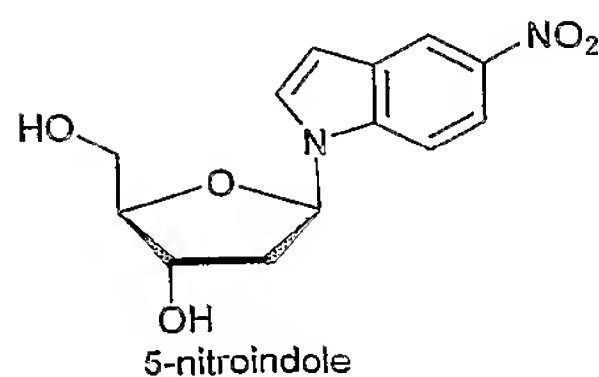
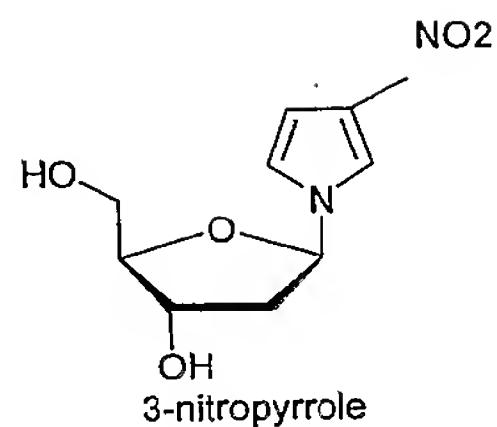


(Difluorotoluene, a nonpolar isostere for thymine, codes specifically and efficiently for adenine in DNA replication. Moran, S. Ren, R. X.-F.; Rumney IV, S.; Kool, E. T. *J. Am. Chem. Soc.*, **1997**, 119, 2056-2057)

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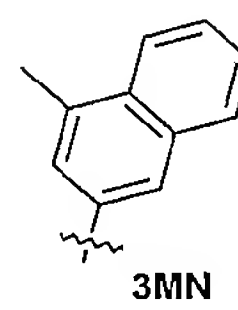
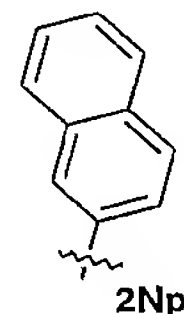
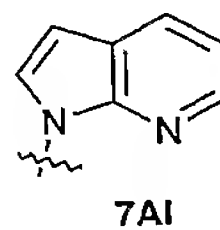
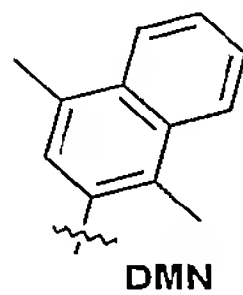
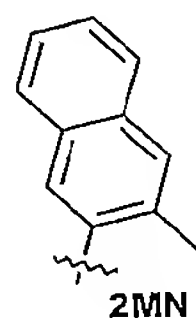
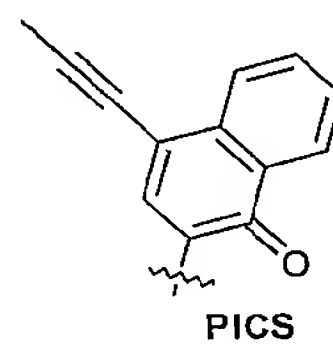
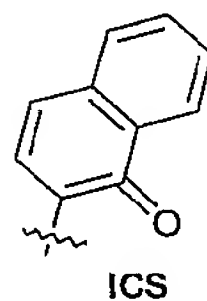
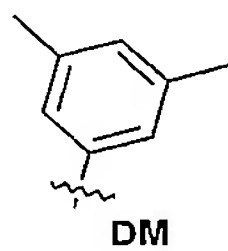
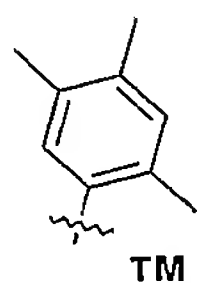
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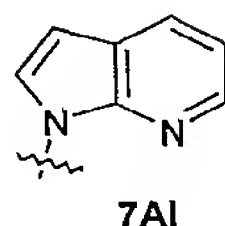
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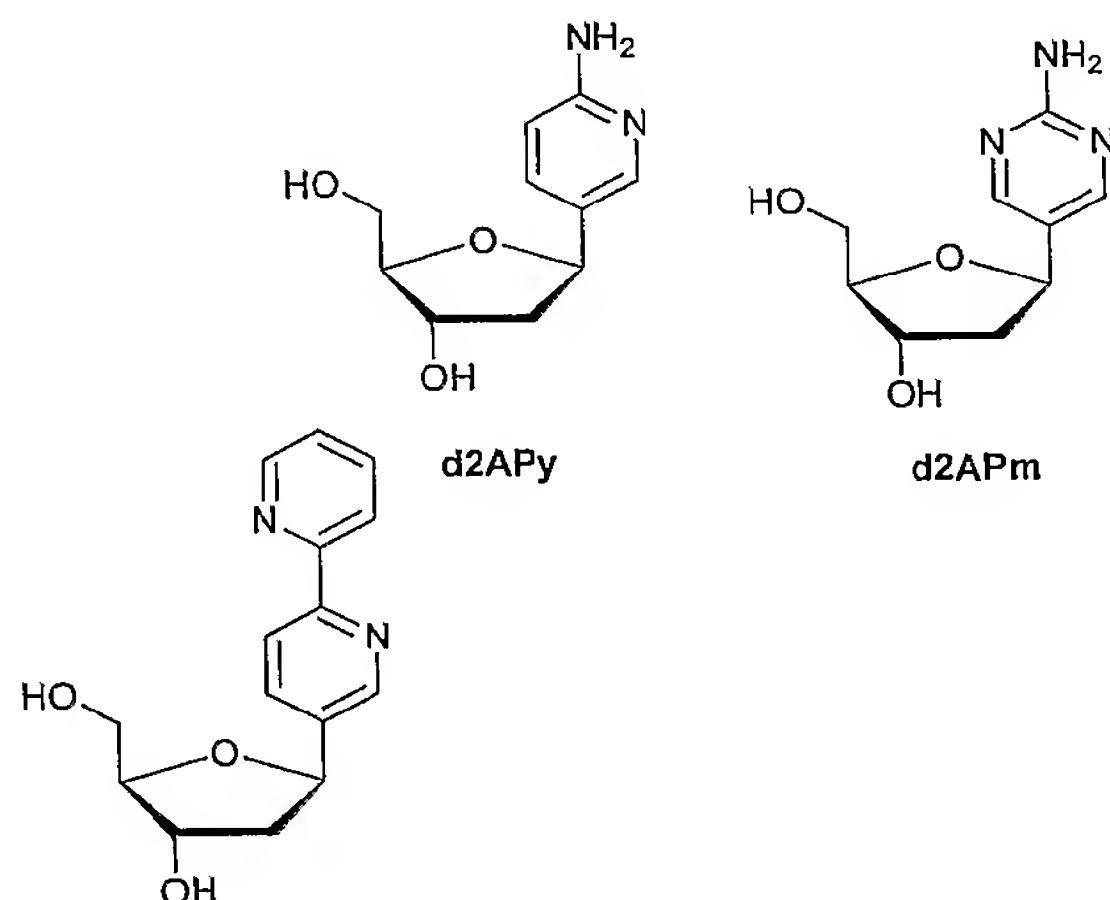


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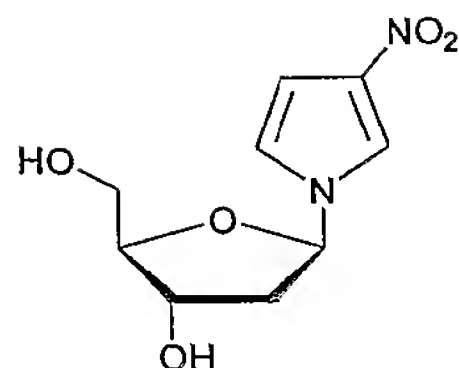
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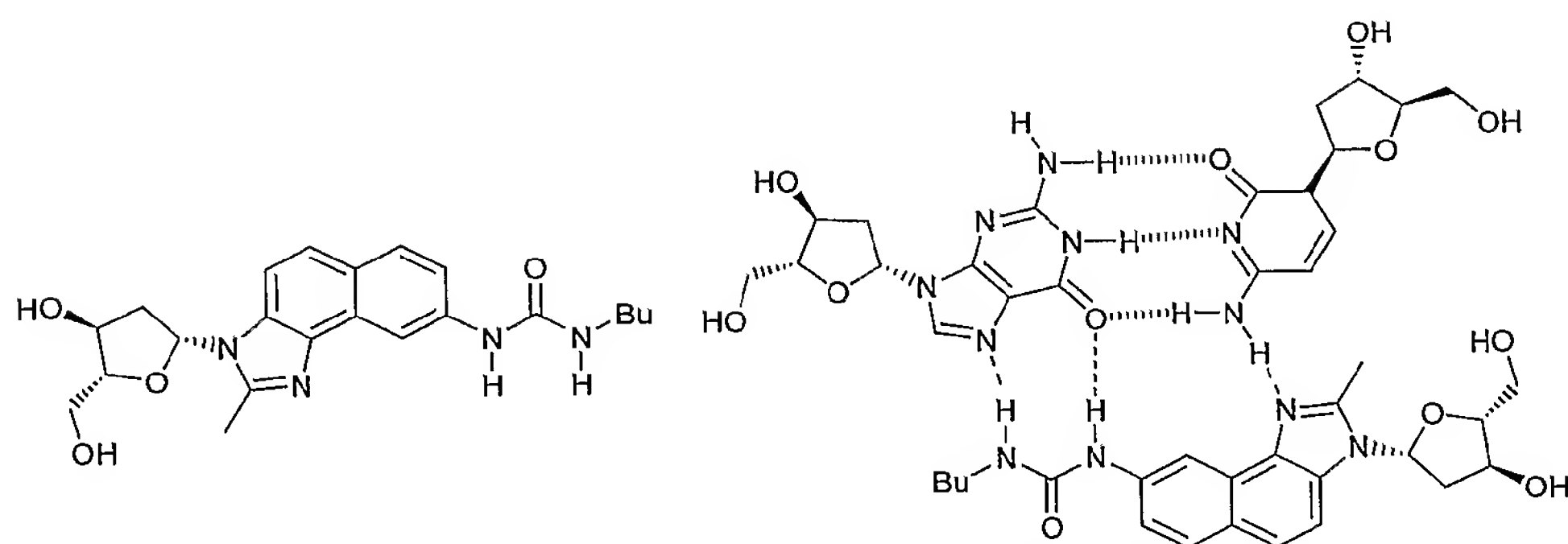


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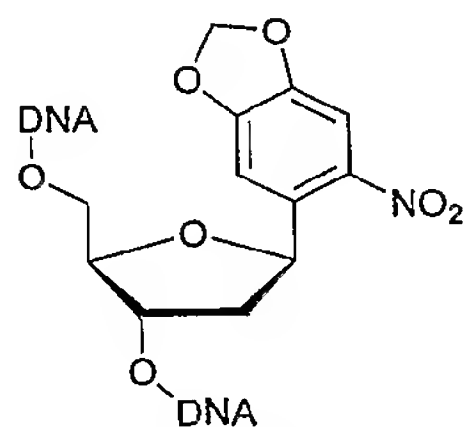




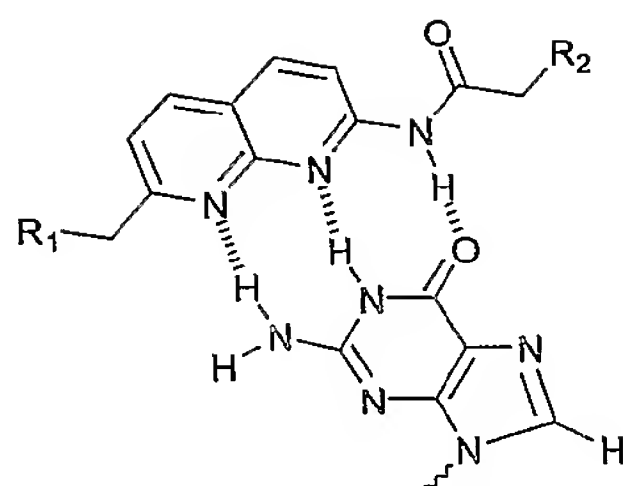
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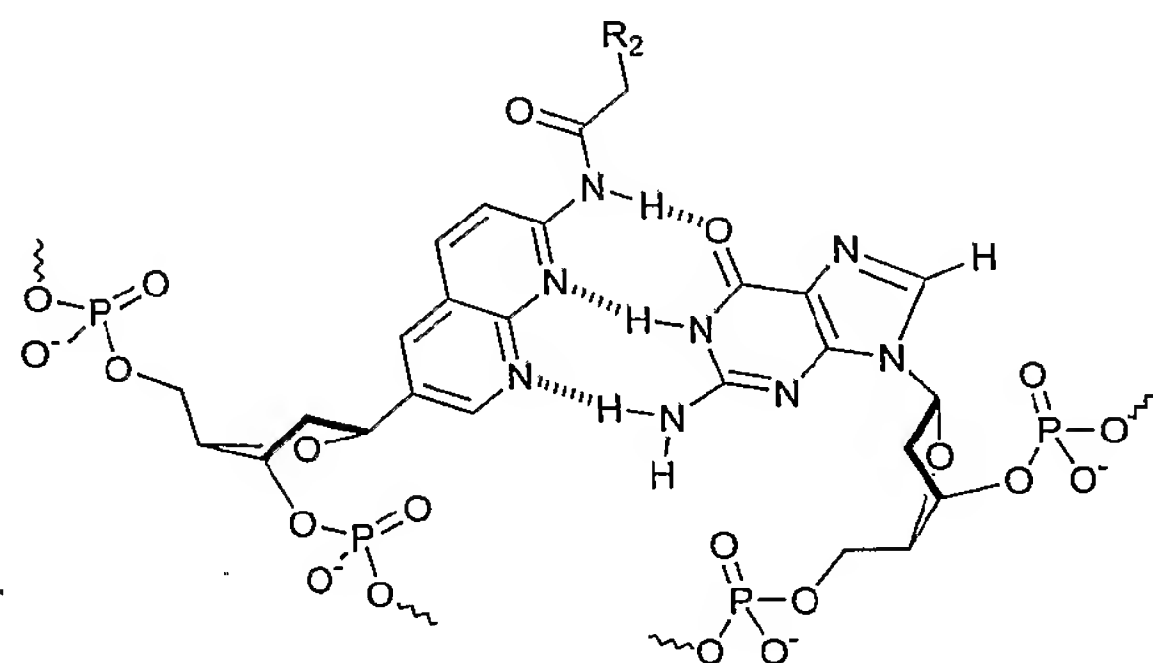
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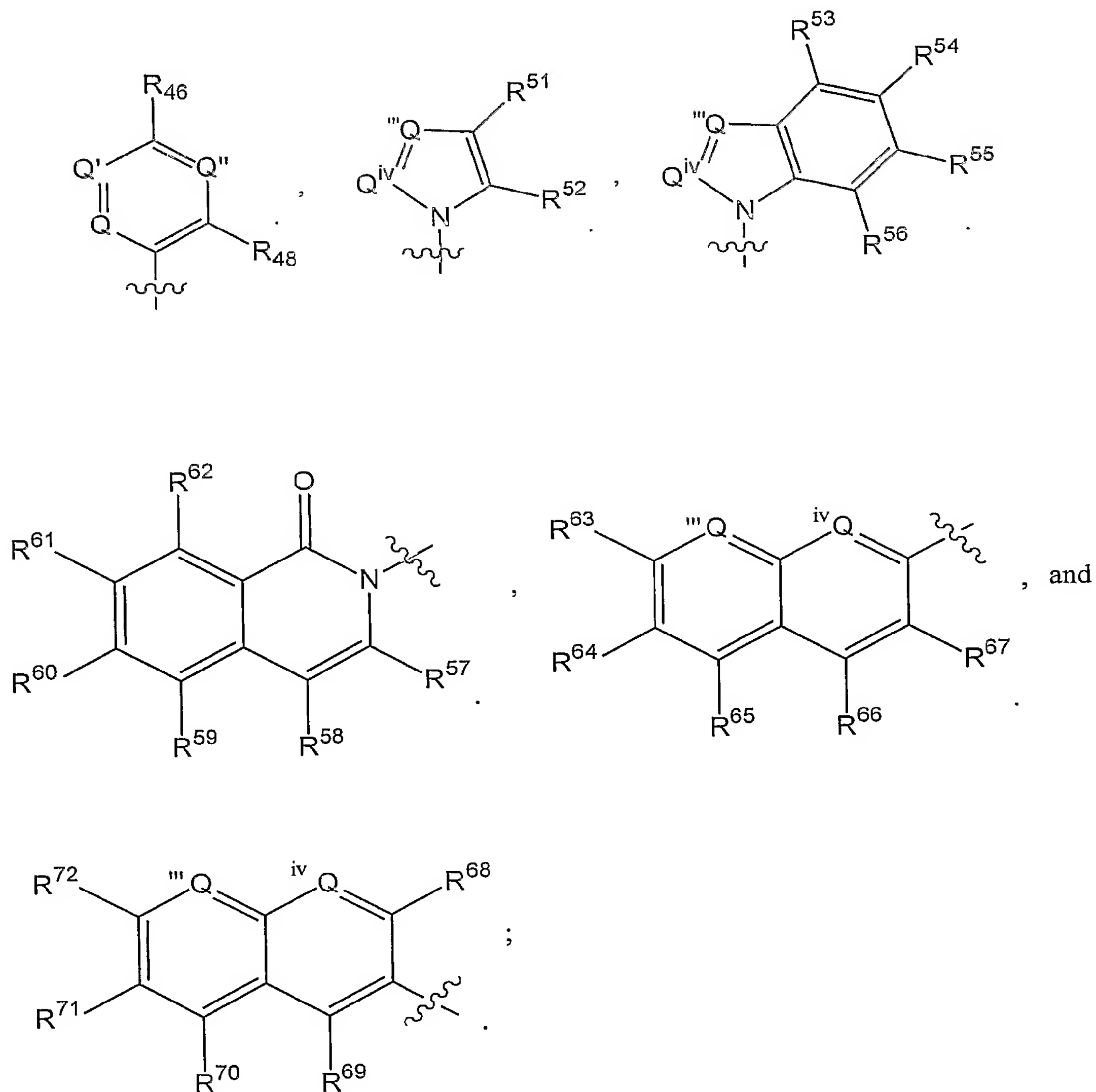
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Other universal bases can have the following formulas:



wherein:

- 5       $Q$  is  $N$  or  $CR^{44}$ ;  
           $Q'$  is  $N$  or  $CR^{45}$ ;  
           $Q''$  is  $N$  or  $CR^{47}$ ;  
           $Q'''$  is  $N$  or  $CR^{49}$ ;  
           $Q^{iv}$  is  $N$  or  $CR^{50}$ ;

$R^{44}$  is hydrogen, halo, hydroxy, nitro, protected hydroxy,  $NH_2$ ,  $NHR^b$ , or  $NR^bR^c$ ,  $C_1$ - $C_6$  alkyl,  $C_6$ - $C_{10}$  aryl,  $C_6$ - $C_{10}$  heteroaryl,  $C_3$ - $C_8$  heterocyclyl, or when taken together with  $R^{45}$  forms  $-OCH_2O-$ ;

$R^{45}$  is hydrogen, halo, hydroxy, nitro, protected hydroxy,  $NH_2$ ,  $NHR^b$ , or  $NR^bR^c$ ,  $C_1$ - $C_6$  alkyl,  $C_6$ - $C_{10}$  aryl,  $C_6$ - $C_{10}$  heteroaryl,  $C_3$ - $C_8$  heterocyclyl, or when taken together with  $R^{44}$  or  $R^{46}$  forms  $-OCH_2O-$ ;

$R^{46}$  is hydrogen, halo, hydroxy, nitro, protected hydroxy,  $NH_2$ ,  $NHR^b$ , or  $NR^bR^c$ ,  $C_1$ - $C_6$  alkyl,  $C_6$ - $C_{10}$  aryl,  $C_6$ - $C_{10}$  heteroaryl,  $C_3$ - $C_8$  heterocyclyl, or when taken together with  $R^{45}$  or  $R^{47}$  forms  $-OCH_2O-$ ;

$R^{47}$  is hydrogen, halo, hydroxy, nitro, protected hydroxy,  $NH_2$ ,  $NHR^b$ , or  $NR^bR^c$ ,  $C_1$ - $C_6$  alkyl,  $C_6$ - $C_{10}$  aryl,  $C_6$ - $C_{10}$  heteroaryl,  $C_3$ - $C_8$  heterocyclyl, or when taken together with  $R^{46}$  or  $R^{48}$  forms  $-OCH_2O-$ ;

$R^{48}$  is hydrogen, halo, hydroxy, nitro, protected hydroxy,  $NH_2$ ,  $NHR^b$ , or  $NR^bR^c$ ,  $C_1$ - $C_6$  alkyl,  $C_6$ - $C_{10}$  aryl,  $C_6$ - $C_{10}$  heteroaryl,  $C_3$ - $C_8$  heterocyclyl, or when taken together with  $R^{47}$  forms  $-OCH_2O-$ ;

$R^{49}$ ,  $R^{50}$ ,  $R^{51}$ ,  $R^{52}$ ,  $R^{53}$ ,  $R^{54}$ ,  $R^{57}$ ,  $R^{58}$ ,  $R^{59}$ ,  $R^{60}$ ,  $R^{61}$ ,  $R^{62}$ ,  $R^{63}$ ,  $R^{64}$ ,  $R^{65}$ ,  $R^{66}$ ,  $R^{67}$ ,  $R^{68}$ ,  $R^{69}$ ,  $R^{70}$ ,  $R^{71}$ , and  $R^{72}$  are each independently selected from hydrogen, halo, hydroxy, nitro, protected hydroxy,  $NH_2$ ,  $NHR^b$ , or  $NR^bR^c$ ,  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkynyl,  $C_6$ - $C_{10}$  aryl,  $C_6$ - $C_{10}$  heteroaryl,  $C_3$ - $C_8$  heterocyclyl,  $NC(O)R^{17}$ , or  $NC(O)R^0$ ;

$R^{55}$  is hydrogen, halo, hydroxy, nitro, protected hydroxy,  $NH_2$ ,  $NHR^b$ , or  $NR^bR^c$ ,  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkynyl,  $C_6$ - $C_{10}$  aryl,  $C_6$ - $C_{10}$  heteroaryl,  $C_3$ - $C_8$  heterocyclyl,  $NC(O)R^{17}$ , or  $NC(O)R^0$ , or when taken together with  $R^{56}$  forms a fused aromatic ring which may be optionally substituted;

$R^{56}$  is hydrogen, halo, hydroxy, nitro, protected hydroxy,  $NH_2$ ,  $NHR^b$ , or  $NR^bR^c$ ,  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkynyl,  $C_6$ - $C_{10}$  aryl,  $C_6$ - $C_{10}$  heteroaryl,  $C_3$ - $C_8$  heterocyclyl,  $NC(O)R^{17}$ , or  $NC(O)R^0$ , or when taken together with  $R^{55}$  forms a fused aromatic ring which may be optionally substituted;

$R^{17}$  is halo,  $NH_2$ ,  $NHR^b$ , or  $NR^bR^c$ ;

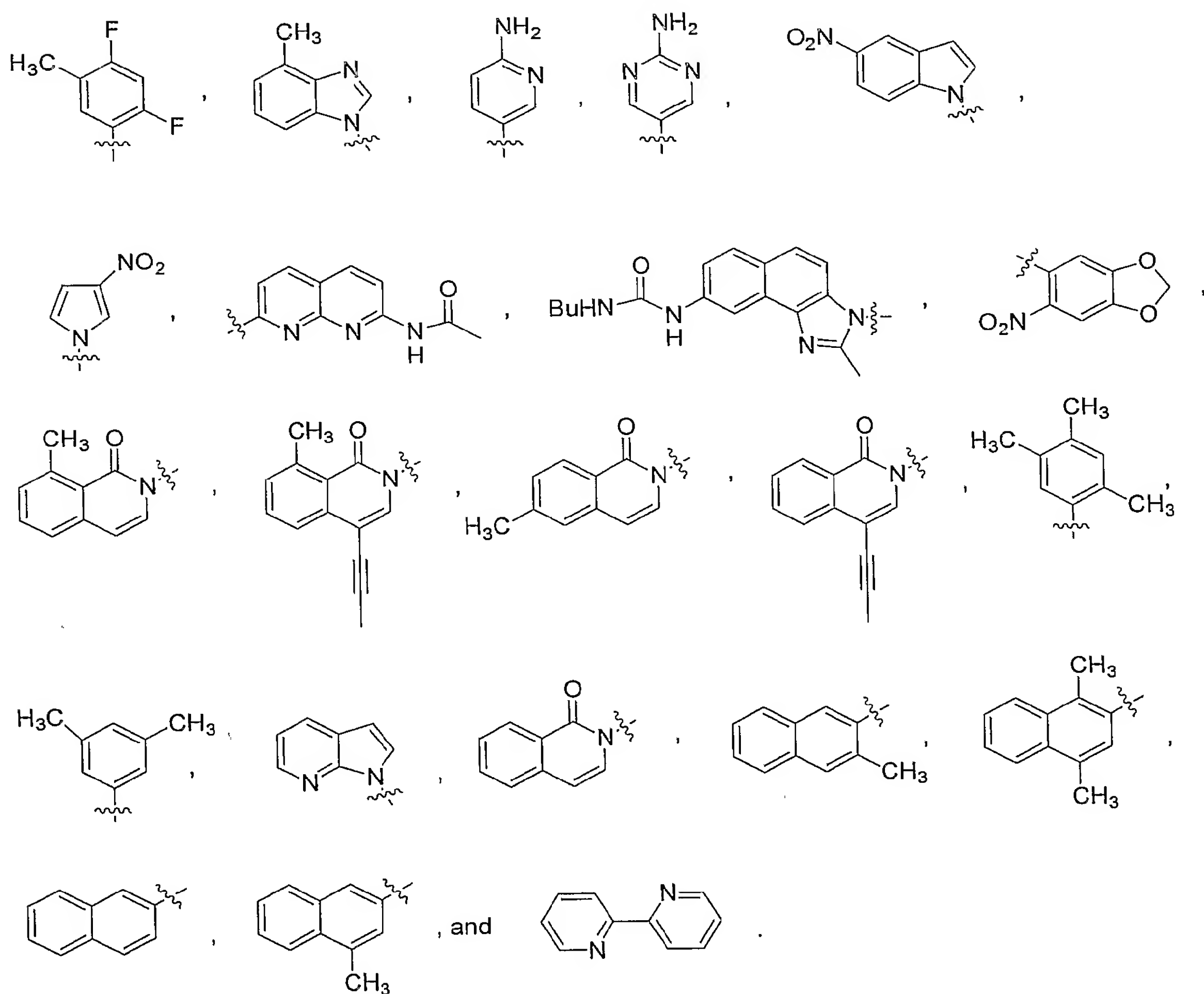
$R^b$  is  $C_1$ - $C_6$  alkyl or a nitrogen protecting group;

$R^c$  is  $C_1$ - $C_6$  alkyl; and

R<sup>o</sup> is alkyl optionally substituted with halo, hydroxy, nitro, protected hydroxy, NH<sub>2</sub>, NHR<sup>b</sup>, or NR<sup>b</sup>R<sup>c</sup>, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>6</sub>-C<sub>10</sub> aryl, C<sub>6</sub>-C<sub>10</sub> heteroaryl, C<sub>3</sub>-C<sub>8</sub> heterocyclyl, NC(O)R<sup>17</sup>, or NC(O)R<sup>o</sup>.

Examples of universal bases include:

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In one aspect, the invention features methods of producing iRNA agents, *e.g.*, sRNA agents, *e.g.* an sRNA agent described herein, having the ability to mediate RNAi. These iRNA agents can be formulated for administration to a subject.

In another aspect, the invention features a method of administering an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, to a subject (*e.g.*, a human subject). The method includes administering a unit dose of the iRNA agent, *e.g.*, a sRNA agent, *e.g.*, double stranded sRNA agent that (a) the double-stranded part is 19-25 nucleotides (nt) long, preferably 21-23 nt, (b) is complementary to a target RNA (*e.g.*, an endogenous or pathogen target RNA), and, optionally, (c) includes at least one 3' overhang 1-5 nucleotide long. In one embodiment, the unit dose is less than 1.4 mg per kg of bodyweight, or less than 10, 5, 2, 1, 0.5, 0.1, 0.05, 0.01, 0.005, 0.001, 0.0005, 0.0001, 0.00005 or 0.00001 mg per kg of bodyweight, and less than 200 nmole of RNA agent (*e.g.* about  $4.4 \times 10^{16}$  copies) per kg of bodyweight, or less than 1500, 750, 300, 150, 75, 15, 7.5, 1.5, 0.75, 0.15, 0.075, 0.015, 0.0075, 0.0015, 0.00075, 0.00015 nmole of RNA agent per kg of bodyweight.

The defined amount can be an amount effective to treat or prevent a disease or disorder, *e.g.*, a disease or disorder associated with the target RNA. The unit dose, for example, can be administered by injection (*e.g.*, intravenous or intramuscular), an inhaled dose, or a topical application. Particularly preferred dosages are less than 2, 1, or 0.1 mg/kg of body weight.

In a preferred embodiment, the unit dose is administered less frequently than once a day, *e.g.*, less than every 2, 4, 8 or 30 days. In another embodiment, the unit dose is not administered with a frequency (*e.g.*, not a regular frequency). For example, the unit dose may be administered a single time.

In one embodiment, the effective dose is administered with other traditional therapeutic modalities. In one embodiment, the subject has a viral infection and the modality is an antiviral agent other than an iRNA agent, *e.g.*, other than a double-stranded iRNA agent, or sRNA agent. In another embodiment, the subject has atherosclerosis and the effective dose of an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, is administered in combination with, *e.g.*, after surgical intervention, *e.g.*, angioplasty.

In one embodiment, a subject is administered an initial dose and one or more maintenance doses of an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent,

(*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof). The maintenance dose or doses are generally lower than the initial dose, *e.g.*, one-half less of the initial dose. A maintenance regimen can include treating the subject  
5 with a dose or doses ranging from 0.01 µg to 1.4 mg/kg of body weight per day, *e.g.*, 10, 1, 0.1, 0.01, 0.001, or 0.00001 mg per kg of bodyweight per day. The maintenance doses are preferably administered no more than once every 5, 10, or 30 days.

In one embodiment, the iRNA agent pharmaceutical composition includes a plurality of iRNA agent species. In another embodiment, the iRNA agent species has sequences that  
10 are non-overlapping and non-adjacent to another species with respect to a naturally occurring target sequence. In another embodiment, the plurality of iRNA agent species is specific for different naturally occurring target genes. In another embodiment, the iRNA agent is allele specific.

The inventors have discovered that iRNA agents described herein can be administered  
15 to mammals, particularly large mammals such as nonhuman primates or humans in a number of ways.

In one embodiment, the administration of the iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, composition is parenteral, *e.g.* intravenous (*e.g.*, as a bolus or as a diffusible infusion), intradermal, intraperitoneal, intramuscular, intrathecal, intraventricular,  
20 intracranial, subcutaneous, transmucosal, buccal, sublingual, endoscopic, rectal, oral, vaginal, topical, pulmonary, intranasal, urethral or ocular. Administration can be provided by the subject or by another person, *e.g.*, a health care provider. The medication can be provided in measured doses or in a dispenser that delivers a metered dose. Selected modes of delivery are discussed in more detail below.

25 The invention provides methods, compositions, and kits, for rectal administration or delivery of iRNA agents described herein.

Accordingly, an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes a an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent,  
30 or precursor thereof) described herein, *e.g.*, a therapeutically effective amount of a iRNA agent described herein, *e.g.*, a iRNA agent having a double stranded region of less than 40,

and preferably less than 30 nucleotides and having one or two 1-3 nucleotide single strand 3' overhangs can be administered rectally, *e.g.*, introduced through the rectum into the lower or upper colon. This approach is particularly useful in the treatment of, inflammatory disorders, disorders characterized by unwanted cell proliferation, *e.g.*, polyps, or colon cancer.

5           In some embodiments the medication is delivered to a site in the colon by introducing a dispensing device, *e.g.*, a flexible, camera-guided device similar to that used for inspection of the colon or removal of polyps, which includes means for delivery of the medication.

          In one embodiment, the rectal administration of the iRNA agent is by means of an enema. The iRNA agent of the enema can be dissolved in a saline or buffered solution.

10           In another embodiment, the rectal administration is by means of a suppository. The suppository can include other ingredients, *e.g.*, an excipient, *e.g.*, cocoa butter or hydropropylmethylcellulose.

          The invention also provides methods, compositions, and kits for oral delivery of iRNA agents described herein.

15           Accordingly, an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) described herein, *e.g.*, a therapeutically effective amount of a iRNA described herein, *e.g.*, a iRNA agent having a double stranded region of less than 40 and  
20           preferably less than 30 nucleotides and having one or two 1-3 nucleotide single strand 3' overhangs can be administered orally.

          Oral administration can be in the form of tablets, capsules, gel capsules, lozenges, troches or liquid syrups. In a preferred embodiment the composition is applied topically to a surface of the oral cavity.

25           The invention also provides methods, compositions, and kits for buccal delivery of iRNA agents described herein.

          Accordingly, an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or  
30           precursor thereof) described herein, *e.g.*, a therapeutically effective amount of iRNA agent having a double stranded region of less than 40 and preferably less than 30 nucleotides and

having one or two 1-3 nucleotide single strand 3' overhangs can be administered to the buccal cavity. The medication can be sprayed into the buccal cavity or applied directly, *e.g.*, in a liquid, solid, or gel form to a surface in the buccal cavity. This administration is particularly desirable for the treatment of inflammations of the buccal cavity, *e.g.*, the gums or tongue, *e.g.*, in one embodiment, the buccal administration is by spraying into the cavity, *e.g.*, without inhalation, from a dispenser, *e.g.*, a metered dose spray dispenser that dispenses the pharmaceutical composition and a propellant.

The invention also provides methods, compositions, and kits for ocular delivery of iRNA agents described herein.

Accordingly, an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) described herein, *e.g.*, a therapeutically effective amount of a iRNA agent described herein, *e.g.*, a sRNA agent having a double stranded region of less than 40 and preferably less than 30 nucleotides and having one or two 1-3 nucleotide single strand 3' overhangs can be administered to ocular tissue.

The medications can be applied to the surface of the eye or nearby tissue, *e.g.*, the inside of the eyelid. It can be applied topically, *e.g.*, by spraying, in drops, as an eyewash, or an ointment. Administration can be provided by the subject or by another person, *e.g.*, a health care provider. The medication can be provided in measured doses or in a dispenser that delivers a metered dose.

The medication can also be administered to the interior of the eye, and can be introduced by a needle or other delivery device which can introduce it to a selected area or structure.

Ocular treatment is particularly desirable for treating inflammation of the eye or nearby tissue.

The invention also provides methods, compositions, and kits for delivery of iRNA agents described herein to or through the skin.

Accordingly, an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or



precursor thereof) described herein, *e.g.*, a therapeutically effective amount of a iRNA agent described herein, *e.g.*, a sRNA agent having a double stranded region of less than 40 and preferably less than 30 nucleotides and one or two 1-3 nucleotide single strand 3' overhangs can be administered directly to the skin.

5           The medication can be applied topically or delivered in a layer of the skin, *e.g.*, by the use of a microneedle or a battery of microneedles which penetrate into the skin, but preferably not into the underlying muscle tissue.

          In one embodiment, the administration of the iRNA agent composition is topical. In another embodiment, topical administration delivers the composition to the dermis or  
10   epidermis of a subject. In other embodiments the topical administration is in the form of transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids or powders. A composition for topical administration can be formulated as a liposome, micelle, emulsion, or other lipophilic molecular assembly.

          In another embodiment, the transdermal administration is applied with at least one  
15   penetration enhancer. In other embodiments, the penetration can be enhanced with iontophoresis, phonophoresis, and sonophoresis. In another aspect, the invention provides methods, compositions, devices, and kits for pulmonary delivery of iRNA agents described herein.

          Accordingly, an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent,  
20   (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) described herein, *e.g.*, a therapeutically effective amount of iRNA agent, *e.g.*, a sRNA agent having a double stranded region of less than 40, preferably less than 30 nucleotides and having one or two 1-3 nucleotide single strand 3' overhangs can be  
25   administered to the pulmonary system. Pulmonary administration can be achieved by inhalation or by the introduction of a delivery device into the pulmonary system, *e.g.*, by introducing a delivery device which can dispense the medication.

          The preferred method of pulmonary delivery is by inhalation. The medication can be provided in a dispenser which delivers the medication, *e.g.*, wet or dry, in a form sufficiently  
30   small such that it can be inhaled. The device can deliver a metered dose of medication. The subject, or another person, can administer the medication.



Pulmonary delivery is effective not only for disorders which directly affect pulmonary tissue, but also for disorders which affect other tissue.

iRNA agents can be formulated as a liquid or nonliquid, *e.g.*, a powder, crystal, or aerosol for pulmonary delivery.

5 In another aspect, the invention provides methods, compositions, devices, and kits for nasal delivery of iRNA agents described herein. Accordingly, an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) described herein, *e.g.*, a  
10 therapeutically effective amount of iRNA agent, *e.g.*, a sRNA agent having a double stranded region of less than 40 and preferably less than 30 nucleotides and having one or two 1-3 nucleotide single strand 3' overhangs can be administered nasally. Nasal administration can be achieved by introduction of a delivery device into the nose, *e.g.*, by introducing a delivery device which can dispense the medication.

15 The preferred method of nasal delivery is by spray, aerosol, liquid, *e.g.*, by drops, of by topical administration to a surface of the nasal cavity. The medication can be provided in a dispenser which delivery of the medication, *e.g.*, wet or dry, in a form sufficiently small such that it can be inhaled. The device can deliver a metered dose of medication. The subject, or another person, can administer the medication.

20 Nasal delivery is effective not only for disorders which directly affect nasal tissue, but also for disorders which affect other tissue

iRNA agents can be formulated as a liquid or nonliquid, *e.g.*, a powder, crystal, or for nasal delivery.

25 In another embodiment, the iRNA agent is packaged in a viral natural capsid or in a chemically or enzymatically produced artificial capsid or structure derived therefrom.

In one aspect, of the invention, the dosage of a pharmaceutical composition including a iRNA agent is administered in order to alleviate the symptoms of a disease state, *e.g.*, cancer or a cardiovascular disease.

30 In another aspect, gene expression in a subject is modulated by administering a pharmaceutical composition including a iRNA agent. In other embodiments, a subject is

treated with the pharmaceutical composition by any of the methods mentioned above. In another embodiment, the subject has cancer.

An iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) composition can be administered as a liposome. For example, the composition can be prepared by a method that includes: (1) contacting a iRNA agent with an amphipathic cationic lipid conjugate in the presence of a detergent; and (2) removing the detergent to form a iRNA agent and cationic lipid complex. In one embodiment, the detergent is cholate, deoxycholate, lauryl sarcosine, octanoyl sucrose, CHAPS (3-[(3-cholamidopropyl)-di-methylamine]-2-hydroxyl-1-propane), novel- $\beta$ -D-glucopyranoside, lauryl dimethylamine oxide, or octylglucoside. The iRNA agent can be an sRNA agent. The method can include preparing a composition that includes a plurality of iRNA agents, *e.g.*, specific for one or more different endogenous target RNAs. The method can include other features described herein.

In another aspect, a subject is treated by administering a defined amount of an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent) composition that is in a powdered form. In one embodiment, the powder is a collection of microparticles. In one embodiment, the powder is a collection of crystalline particles. The composition can include a plurality of iRNA agents, *e.g.*, specific for one or more different endogenous target RNAs. The method can include other features described herein.

In one aspect, a subject is treated by administering a defined amount of a iRNA agent composition that is prepared by a method that includes spray-drying, *i.e.* atomizing a liquid solution, emulsion, or suspension, immediately exposing the droplets to a drying gas, and collecting the resulting porous powder particles. The composition can include a plurality of iRNA agents, *e.g.*, specific for one or more different endogenous target RNAs. The method can include other features described herein.

In one aspect, the iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or

precursor thereof), is provided in a powdered, crystallized or other finely divided form, with or without a carrier, *e.g.*, a micro- or nano-particle suitable for inhalation or other pulmonary delivery. In one embodiment, this includes providing an aerosol preparation, *e.g.*, an aerosolized spray-dried composition. The aerosol composition can be provided in and/or  
5 dispensed by a metered dose delivery device.

In another aspect, a subject is treated for a condition treatable by inhalation. In one embodiment, this method includes aerosolizing a spray-dried iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-  
10 stranded iRNA agent, or sRNA agent, or precursor thereof) composition and inhaling the aerosolized composition. The iRNA agent can be an sRNA. The composition can include a plurality of iRNA agents, *e.g.*, specific for one or more different endogenous target RNAs. The method can include other features described herein.

In another aspect, the invention features a method of treating a subject that includes:  
15 administering a composition including an effective/defined amount of an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof), wherein the composition is prepared by a method that includes spray-drying, lyophilization, vacuum drying,  
20 evaporation, fluid bed drying, or a combination of these techniques

In another aspect, the invention features a method that includes: evaluating a parameter related to the abundance of a transcript in a cell of a subject; comparing the evaluated parameter to a reference value; and if the evaluated parameter has a preselected relationship to the reference value (*e.g.*, it is greater), administering a iRNA agent (or a  
25 precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes a iRNA agent or precursor thereof) to the subject. In one embodiment, the iRNA agent includes a sequence that is complementary to the evaluated transcript. For example, the parameter can be a direct measure of transcript levels, a measure of a protein level, a disease or disorder symptom or characterization (*e.g.*, rate of cell proliferation and/or  
30 tumor mass, viral load,)

In another aspect, the invention features a method that includes: administering a first amount of a composition that comprises an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) to a subject, wherein the iRNA agent includes a strand substantially complementary to a target nucleic acid; evaluating an activity associated with a protein encoded by the target nucleic acid; wherein the evaluation is used to determine if a second amount should be administered. In a preferred embodiment the method includes administering a second amount of the composition, wherein the timing of administration or dosage of the second amount is a function of the evaluating. The method can include other features described herein.

In another aspect, the invention features a method of administering a source of a double-stranded iRNA agent (ds iRNA agent) to a subject. The method includes administering or implanting a source of a ds iRNA agent, *e.g.*, a sRNA agent, that (a) includes a double-stranded region that is 19-25 nucleotides long, preferably 21-23 nucleotides, (b) is complementary to a target RNA (*e.g.*, an endogenous RNA or a pathogen RNA), and, optionally, (c) includes at least one 3' overhang 1-5 nt long. In one embodiment, the source releases ds iRNA agent over time, *e.g.* the source is a controlled or a slow release source, *e.g.*, a microparticle that gradually releases the ds iRNA agent. In another embodiment, the source is a pump, *e.g.*, a pump that includes a sensor or a pump that can release one or more unit doses.

In one aspect, the invention features a pharmaceutical composition that includes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) including a nucleotide sequence complementary to a target RNA, *e.g.*, substantially and/or exactly complementary. The target RNA can be a transcript of an endogenous human gene. In one embodiment, the iRNA agent (a) is 19-25 nucleotides long, preferably 21-23 nucleotides, (b) is complementary to an endogenous target RNA, and, optionally, (c) includes at least one 3' overhang 1-5 nt long. In one embodiment, the pharmaceutical composition can be an emulsion, microemulsion, cream, jelly, or liposome.



In one example the pharmaceutical composition includes an iRNA agent mixed with a topical delivery agent. The topical delivery agent can be a plurality of microscopic vesicles. The microscopic vesicles can be liposomes. In a preferred embodiment the liposomes are cationic liposomes.

5 In another aspect, the pharmaceutical composition includes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) admixed with a topical penetration enhancer. In one embodiment, the topical penetration enhancer is a fatty acid.  
10 The fatty acid can be arachidonic acid, oleic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprinate, tricaprinate, monolein, dilaurin, glyceryl 1-monocaprinate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a C<sub>1-10</sub> alkyl ester, monoglyceride, diglyceride or pharmaceutically acceptable salt thereof.

15 In another embodiment, the topical penetration enhancer is a bile salt. The bile salt can be cholic acid, dehydrocholic acid, deoxycholic acid, glucolic acid, glycholic acid, glycodeoxycholic acid, taurocholic acid, taurodeoxycholic acid, chenodeoxycholic acid, ursodeoxycholic acid, sodium tauro-24,25-dihydro-fusidate, sodium glycodihydrofusidate, polyoxyethylene-9-lauryl ether or a pharmaceutically acceptable salt thereof.

20 In another embodiment, the penetration enhancer is a chelating agent. The chelating agent can be EDTA, citric acid, a salicylate, a N-acyl derivative of collagen, laurth-9, an N-amino acyl derivative of a beta-diketone or a mixture thereof.

In another embodiment, the penetration enhancer is a surfactant, *e.g.*, an ionic or nonionic surfactant. The surfactant can be sodium lauryl sulfate, polyoxyethylene-9-lauryl  
25 ether, polyoxyethylene-20-cetyl ether, a perfluorchemical emulsion or mixture thereof.

In another embodiment, the penetration enhancer can be selected from a group consisting of unsaturated cyclic ureas, 1-alkyl-alkones, 1-alkenylazacyclo-alkanones, steroidal anti-inflammatory agents and mixtures thereof. In yet another embodiment the penetration enhancer can be a glycol, a pyrrol, an azone, or a terpenes.

30 In one aspect, the invention features a pharmaceutical composition including an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a



larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) in a form suitable for oral delivery. In one embodiment, oral delivery can be used to deliver an iRNA agent composition to a cell or a region of the gastro-intestinal tract, *e.g.*, small intestine, colon (*e.g.*, to treat a colon cancer), and so forth. The oral delivery form can be tablets, capsules or gel capsules. In one embodiment, the iRNA agent of the pharmaceutical composition modulates expression of a cellular adhesion protein, modulates a rate of cellular proliferation, or has biological activity against eukaryotic pathogens or retroviruses. In another embodiment, the pharmaceutical composition includes an enteric material that substantially prevents dissolution of the tablets, capsules or gel capsules in a mammalian stomach. In a preferred embodiment the enteric material is a coating. The coating can be acetate phthalate, propylene glycol, sorbitan monoleate, cellulose acetate trimellitate, hydroxy propyl methylcellulose phthalate or cellulose acetate phthalate.

In another embodiment, the oral dosage form of the pharmaceutical composition includes a penetration enhancer. The penetration enhancer can be a bile salt or a fatty acid. The bile salt can be ursodeoxycholic acid, chenodeoxycholic acid, and salts thereof. The fatty acid can be capric acid, lauric acid, and salts thereof.

In another embodiment, the oral dosage form of the pharmaceutical composition includes an excipient. In one example the excipient is polyethyleneglycol. In another example the excipient is precinol.

In another embodiment, the oral dosage form of the pharmaceutical composition includes a plasticizer. The plasticizer can be diethyl phthalate, triacetin dibutyl sebacate, dibutyl phthalate or triethyl citrate.

In one aspect, the invention features a pharmaceutical composition including an iRNA agent and a delivery vehicle. In one embodiment, the iRNA agent is (a) is 19-25 nucleotides long, preferably 21-23 nucleotides, (b) is complementary to an endogenous target RNA, and, optionally, (c) includes at least one 3' overhang 1-5 nucleotides long.

In one embodiment, the delivery vehicle can deliver an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) to a cell by a topical route of

administration. The delivery vehicle can be microscopic vesicles. In one example the microscopic vesicles are liposomes. In a preferred embodiment the liposomes are cationic liposomes. In another example the microscopic vesicles are micelles.

In one aspect, the invention features a method for making a pharmaceutical composition, the method including: (1) contacting an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent) with a amphipathic cationic lipid conjugate in the presence of a detergent; and (2) removing the detergent to form a iRNA agent and cationic lipid complex.

In another aspect, the invention features a pharmaceutical composition produced by a method including: (1) contacting an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent) with a amphipathic cationic lipid conjugate in the presence of a detergent; and (2) removing the detergent to form a iRNA agent and cationic lipid complex. In one embodiment, the detergent is cholate, deoxycholate, lauryl sarcosine, octanoyl sucrose, CHAPS (3-[(3-cholamidopropyl)-di-methylamine]-2-hydroxyl-1-propane), novel- $\beta$ -D-glucopyranoside, lauryl dimethylamine oxide, or octylglucoside. In another embodiment, the amphipathic cationic lipid conjugate is biodegradable. In yet another embodiment the pharmaceutical composition includes a targeting ligand.

In one aspect, the invention features a pharmaceutical composition including an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) in an injectable dosage form. In one embodiment, the injectable dosage form of the pharmaceutical composition includes sterile aqueous solutions or dispersions and sterile powders. In a preferred embodiment the sterile solution can include a diluent such as water; saline solution; fixed oils, polyethylene glycols, glycerin, or propylene glycol.

In one aspect, the invention features a pharmaceutical composition including an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) in oral dosage form. In one embodiment, the oral dosage form is selected from the group

consisting of tablets, capsules and gel capsules. In another embodiment, the pharmaceutical composition includes an enteric material that substantially prevents dissolution of the tablets, capsules or gel capsules in a mammalian stomach. In a preferred embodiment the enteric material is a coating. The coating can be acetate phthalate, propylene glycol, sorbitan  
5 monoleate, cellulose acetate trimellitate, hydroxy propyl methyl cellulose phthalate or cellulose acetate phthalate. In one embodiment, the oral dosage form of the pharmaceutical composition includes a penetration enhancer, *e.g.*, a penetration enhancer described herein.

In another embodiment, the oral dosage form of the pharmaceutical composition includes an excipient. In one example the excipient is polyethyleneglycol. In another  
10 example the excipient is precirol.

In another embodiment, the oral dosage form of the pharmaceutical composition includes a plasticizer. The plasticizer can be diethyl phthalate, triacetin dibutyl sebacate, dibutyl phthalate or triethyl citrate.

In one aspect, the invention features a pharmaceutical composition including an  
15 iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) in a rectal dosage form. In one embodiment, the rectal dosage form is an enema. In another embodiment, the rectal dosage form is a suppository.

In one aspect, the invention features a pharmaceutical composition including an  
20 iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) in a vaginal dosage form. In one embodiment, the vaginal dosage form is a suppository. In  
25 another embodiment, the vaginal dosage form is a foam, cream, or gel.

In one aspect, the invention features a pharmaceutical composition including an  
iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) in a  
30 pulmonary or nasal dosage form. In one embodiment, the iRNA agent is incorporated into a particle, *e.g.*, a macroparticle, *e.g.*, a microsphere. The particle can be produced by spray

drying, lyophilization, evaporation, fluid bed drying, vacuum drying, or a combination thereof. The microsphere can be formulated as a suspension, a powder, or an implantable solid.

In one aspect, the invention features a spray-dried iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) composition suitable for inhalation by a subject, including: (a) a therapeutically effective amount of a iRNA agent suitable for treating a condition in the subject by inhalation; (b) a pharmaceutically acceptable excipient selected from the group consisting of carbohydrates and amino acids; and (c) optionally, a dispersibility-enhancing amount of a physiologically-acceptable, water-soluble polypeptide.

In one embodiment, the excipient is a carbohydrate. The carbohydrate can be selected from the group consisting of monosaccharides, disaccharides, trisaccharides, and polysaccharides. In a preferred embodiment the carbohydrate is a monosaccharide selected from the group consisting of dextrose, galactose, mannitol, D-mannose, sorbitol, and sorbose. In another preferred embodiment the carbohydrate is a disaccharide selected from the group consisting of lactose, maltose, sucrose, and trehalose.

In another embodiment, the excipient is an amino acid. In one embodiment, the amino acid is a hydrophobic amino acid. In a preferred embodiment the hydrophobic amino acid is selected from the group consisting of alanine, isoleucine, leucine, methionine, phenylalanine, proline, tryptophan, and valine. In yet another embodiment the amino acid is a polar amino acid. In a preferred embodiment the amino acid is selected from the group consisting of arginine, histidine, lysine, cysteine, glycine, glutamine, serine, threonine, tyrosine, aspartic acid and glutamic acid.

In one embodiment, the dispersibility-enhancing polypeptide is selected from the group consisting of human serum albumin,  $\alpha$ -lactalbumin, trypsinogen, and polyalanine.

In one embodiment, the spray-dried iRNA agent composition includes particles having a mass median diameter (MMD) of less than 10 microns. In another embodiment, the spray-dried iRNA agent composition includes particles having a mass median diameter of less than 5 microns. In yet another embodiment the spray-dried iRNA agent composition



includes particles having a mass median aerodynamic diameter (MMAD) of less than 5 microns.

In certain other aspects, the invention provides kits that include a suitable container containing a pharmaceutical formulation of an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof). In certain embodiments the individual components of the pharmaceutical formulation may be provided in one container. Alternatively, it may be desirable to provide the components of the pharmaceutical formulation separately in two or more containers, *e.g.*, one container for an iRNA agent preparation, and at least another for a carrier compound. The kit may be packaged in a number of different configurations such as one or more containers in a single box. The different components can be combined, *e.g.*, according to instructions provided with the kit. The components can be combined according to a method described herein, *e.g.*, to prepare and administer a pharmaceutical composition. The kit can also include a delivery device.

In another aspect, the invention features a device, *e.g.*, an implantable device, wherein the device can dispense or administer a composition that includes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof), *e.g.*, a iRNA agent that silences an endogenous transcript. In one embodiment, the device is coated with the composition. In another embodiment the iRNA agent is disposed within the device. In another embodiment, the device includes a mechanism to dispense a unit dose of the composition. In other embodiments the device releases the composition continuously, *e.g.*, by diffusion. Exemplary devices include stents, catheters, pumps, artificial organs or organ components (*e.g.*, artificial heart, a heart valve, etc.), and sutures.

As used herein, the term "crystalline" describes a solid having the structure or characteristics of a crystal, *i.e.*, particles of three-dimensional structure in which the plane faces intersect at definite angles and in which there is a regular internal structure. The compositions of the invention may have different crystalline forms. Crystalline forms can be prepared by a variety of methods, including, for example, spray drying.



As used herein, “specifically hybridizable” and “complementary” are terms which are used to indicate a sufficient degree of complementarity such that stable and specific binding occurs between a compound of the invention and a target RNA molecule. Specific binding requires a sufficient degree of complementarity to avoid non-specific binding of the oligomeric compound to non-target sequences under conditions in which specific binding is desired, *i.e.*, under physiological conditions in the case of *in vivo* assays or therapeutic treatment, or in the case of *in vitro* assays, under conditions in which the assays are performed. The non-target sequences typically differ by at least 5 nucleotides.

In one embodiment, an iRNA agent is “sufficiently complementary” to a target RNA, *e.g.*, a target mRNA, such that the iRNA agent silences production of protein encoded by the target mRNA. In another embodiment, the iRNA agent is “exactly complementary” to a target RNA, *e.g.*, the target RNA and the iRNA agent anneal, preferably to form a hybrid made exclusively of Watson-Crick basepairs in the region of exact complementarity. A “sufficiently complementary” target RNA can include an internal region (*e.g.*, of at least 10 nucleotides) that is exactly complementary to a target RNA. Moreover, in some embodiments, the iRNA agent specifically discriminates a single-nucleotide difference. In this case, the iRNA agent only mediates RNAi if exact complementarity is found in the region (*e.g.*, within 7 nucleotides of) the single-nucleotide difference.

As used herein, the term “oligonucleotide” refers to a nucleic acid molecule (RNA or DNA) preferably of length less than 100, 200, 300, or 400 nucleotides.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. The materials, methods, and examples are illustrative only and not intended to be limiting. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, useful methods and materials are described below. Other features and advantages of the invention will be apparent from the accompanying drawings and description, and from the claims. The contents of all references, pending patent applications and published patents, cited throughout this application are hereby expressly incorporated by reference. In case of conflict, the present specification, including definitions, will control.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a structural representation of base pairing in pseudocomplementary siRNA<sup>2</sup>.

FIG. 2 is a schematic representation of dual targeting siRNAs designed to target the HCV genome.

5 FIG. 3 is a schematic representation of pseudocomplementary, bifunctional siRNAs designed to target the HCV genome.

FIG. 4 is a general synthetic scheme for incorporation of RRMS monomers into an oligonucleotide.

FIG. 5 is a table of representative RRMS carriers. Panel 1 shows pyrroline-based  
10 RRMSs; panel 2 shows 3-hydroxyproline-based RRMSs; panel 3 shows piperidine-based RRMSs; panel 4 shows morpholine and piperazine-based RRMSs; and panel 5 shows decalin-based RRMSs. R1 is succinate or phosphoramidate and R2 is H or a conjugate ligand.

FIG. 6A. is a graph depicting levels of luciferase mRNA in livers of CMV-Luc mice  
15 (Xanogen) following intravenous injection (iv) of buffer or siRNA into the tail vein. Each bar represents data from one mouse. RNA levels were quantified by QuantiGene Assay (Genospectra, Inc.; Fremont, CA)). The Y axis represents chemiluminescence values in counts per second (CPS).

FIG. 6B. is a graph depicting levels of luciferase mRNA in livers of CMV-Luc mice  
20 (Xanogen). The values are averaged from the data depicted in FIG. 6A.

FIG. 7 is a graph depicting the pharmacokinetics of cholesterol-conjugated and unconjugated siRNA. The diamonds represent the amount of unconjugated <sup>33</sup>P-labeled siRNA (ALN-3000) in mouse plasma over time; the squares represent the amount of cholesterol-conjugated <sup>33</sup>P-labeled siRNA (ALN-3001) in mouse plasma over time. "L1163"  
25 is equivalent to ALN3000; "L1163Chol" is equivalent to ALN-3001.

## DETAILED DESCRIPTION

Double-stranded (dsRNA) directs the sequence-specific silencing of mRNA through a process known as RNA interference (RNAi). The process occurs in a wide variety of  
30 organisms, including mammals and other vertebrates.

It has been demonstrated that 21-23 nt fragments of dsRNA are sequence-specific mediators of RNA silencing, *e.g.*, by causing RNA degradation. While not wishing to be bound by theory, it may be that a molecular signal, which may be merely the specific length of the fragments, present in these 21-23 nt fragments recruits cellular factors that mediate RNAi. Described herein are methods for preparing and administering these 21-23 nt fragments, and other iRNAs agents, and their use for specifically inactivating gene function. The use of iRNAs agents (or recombinantly produced or chemically synthesized oligonucleotides of the same or similar nature) enables the targeting of specific mRNAs for silencing in mammalian cells. In addition, longer dsRNA agent fragments can also be used, *e.g.*, as described below.

Although, in mammalian cells, long dsRNAs can induce the interferon response which is frequently deleterious, sRNAs do not trigger the interferon response, at least not to an extent that is deleterious to the cell and host. In particular, the length of the iRNA agent strands in an sRNA agent can be less than 31, 30, 28, 25, or 23 nt, *e.g.*, sufficiently short to avoid inducing a deleterious interferon response. Thus, the administration of a composition of sRNA agent (*e.g.*, formulated as described herein) to a mammalian cell can be used to silence expression of a target gene while circumventing the interferon response. Further, use of a discrete species of iRNA agent can be used to selectively target one allele of a target gene, *e.g.*, in a subject heterozygous for the allele.

Moreover, in one embodiment, a mammalian cell is treated with an iRNA agent that disrupts a component of the interferon response, *e.g.*, double stranded RNA (dsRNA)-activated protein kinase PKR. Such a cell can be treated with a second iRNA agent that includes a sequence complementary to a target RNA and that has a length that might otherwise trigger the interferon response.

In a typical embodiment, the subject is a mammal such as a cow, horse, mouse, rat, dog, pig, goat, or a primate. The subject can be a dairy mammal (*e.g.*, a cow, or goat) or other farmed animal (*e.g.*, a chicken, turkey, sheep, pig, fish, shrimp). In a much preferred embodiment, the subject is a human, *e.g.*, a normal individual or an individual that has, is diagnosed with, or is predicted to have a disease or disorder.

Further, because iRNA agent mediated silencing persists for several days after administering the iRNA agent composition, in many instances, it is possible to administer the

composition with a frequency of less than once per day, or, for some instances, only once for the entire therapeutic regimen. For example, treatment of some cancer cells may be mediated by a single bolus administration, whereas a chronic viral infection may require regular administration, *e.g.*, once per week or once per month.

5 A number of exemplary routes of delivery are described that can be used to administer an iRNA agent to a subject. In addition, the iRNA agent can be formulated according to an exemplary method described herein.

### iRNA AGENT STRUCTURE

10

Described herein are isolated iRNA agents, *e.g.*, RNA molecules, (double-stranded; single-stranded) that mediate RNAi. The iRNA agents preferably mediate RNAi with respect to an endogenous gene of a subject or to a gene of a pathogen.

15 An "RNA agent" as used herein, is an unmodified RNA, modified RNA, or nucleoside surrogate, all of which are defined herein (see, *e.g.*, the section below entitled RNA Agents). While numerous modified RNAs and nucleoside surrogates are described, preferred examples include those which have greater resistance to nuclease degradation than do unmodified RNAs. Preferred examples include those which have a 2' sugar modification, a modification in a single strand overhang, preferably a 3' single strand overhang, or,  
20 particularly if single stranded, a 5' modification which includes one or more phosphate groups or one or more analogs of a phosphate group.

An "iRNA agent" as used herein, is an RNA agent which can, or which can be cleaved into an RNA agent which can, down regulate the expression of a target gene, preferably an endogenous or pathogen target RNA. While not wishing to be bound by  
25 theory, an iRNA agent may act by one or more of a number of mechanisms, including post-transcriptional cleavage of a target mRNA sometimes referred to in the art as RNAi, or pre-transcriptional or pre-translational mechanisms. An iRNA agent can include a single strand or can include more than one strands, *e.g.*, it can be a double stranded iRNA agent. If the iRNA agent is a single strand it is particularly preferred that it include a 5' modification  
30 which includes one or more phosphate groups or one or more analogs of a phosphate group.

The iRNA agent should include a region of sufficient homology to the target gene, and be of sufficient length in terms of nucleotides, such that the iRNA agent, or a fragment

thereof, can mediate down regulation of the target gene. (For ease of exposition the term nucleotide or ribonucleotide is sometimes used herein in reference to one or more monomeric subunits of an RNA agent. It will be understood herein that the usage of the term “ribonucleotide” or “nucleotide”, herein can, in the case of a modified RNA or nucleotide surrogate, also refer to a modified nucleotide, or surrogate replacement moiety at one or more positions.) Thus, the iRNA agent is or includes a region which is at least partially, and in some embodiments fully, complementary to the target RNA. It is not necessary that there be perfect complementarity between the iRNA agent and the target, but the correspondence must be sufficient to enable the iRNA agent, or a cleavage product thereof, to direct sequence specific silencing, *e.g.*, by RNAi cleavage of the target RNA, *e.g.*, mRNA.

Complementarity, or degree of homology with the target strand, is most critical in the antisense strand. While perfect complementarity, particularly in the antisense strand, is often desired some embodiments can include, particularly in the antisense strand, one or more but preferably 6, 5, 4, 3, 2, or fewer mismatches (with respect to the target RNA). The mismatches, particularly in the antisense strand, are most tolerated in the terminal regions and if present are preferably in a terminal region or regions, *e.g.*, within 6, 5, 4, or 3 nucleotides of the 5' and/or 3' terminus. The sense strand need only be sufficiently complementary with the antisense strand to maintain the over all double strand character of the molecule.

As discussed elsewhere herein, an iRNA agent will often be modified or include nucleoside surrogates in addition to the RRMS. Single stranded regions of an iRNA agent will often be modified or include nucleoside surrogates, *e.g.*, the unpaired region or regions of a hairpin structure, *e.g.*, a region which links two complementary regions, can have modifications or nucleoside surrogates. Modification to stabilize one or more 3'- or 5'- terminus of an iRNA agent, *e.g.*, against exonucleases, or to favor the antisense sRNA agent to enter into RISC are also favored. Modifications can include C3 (or C6, C7, C12) amino linkers, thiol linkers, carboxyl linkers, non-nucleotidic spacers (C3, C6, C9, C12, abasic, triethylene glycol, hexaethylene glycol), special biotin or fluorescein reagents that come as phosphoramidites and that have another DMT-protected hydroxyl group, allowing multiple couplings during RNA synthesis.



iRNA agents include: molecules that are long enough to trigger the interferon response (which can be cleaved by Dicer (Bernstein *et al.* 2001. Nature, 409:363-366) and enter a RISC (RNAi-induced silencing complex)); and, molecules which are sufficiently short that they do not trigger the interferon response (which molecules can also be cleaved by Dicer and/or enter a RISC), *e.g.*, molecules which are of a size which allows entry into a RISC, *e.g.*, molecules which resemble Dicer-cleavage products. Molecules that are short enough that they do not trigger an interferon response are termed sRNA agents or shorter iRNA agents herein. “sRNA agent or shorter iRNA agent” as used herein, refers to an iRNA agent, *e.g.*, a double stranded RNA agent or single strand agent, that is sufficiently short that it does not induce a deleterious interferon response in a human cell, *e.g.*, it has a duplexed region of less than 60 but preferably less than 50, 40, or 30 nucleotide pairs. The sRNA agent, or a cleavage product thereof, can down regulate a target gene, *e.g.*, by inducing RNAi with respect to a target RNA, preferably an endogenous or pathogen target RNA.

Each strand of an sRNA agent can be equal to or less than 30, 25, 24, 23, 22, 21, or 20 nucleotides in length. The strand is preferably at least 19 nucleotides in length. For example, each strand can be between 21 and 25 nucleotides in length. Preferred sRNA agents have a duplex region of 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleotide pairs, and one or more overhangs, preferably one or two 3' overhangs, of 2- 3 nucleotides.

In addition to homology to target RNA and the ability to down regulate a target gene, an iRNA agent will preferably have one or more of the following properties:

- (1) it will be of the Formula 1, 2, 3, or 4 set out in the RNA Agent section below;
- (2) if single stranded it will have a 5' modification which includes one or more phosphate groups or one or more analogs of a phosphate group;
- (3) it will, despite modifications, even to a very large number, or all of the nucleosides, have an antisense strand that can present bases (or modified bases) in the proper three dimensional framework so as to be able to form correct base pairing and form a duplex structure with a homologous target RNA which is sufficient to allow down regulation of the target, *e.g.*, by cleavage of the target RNA;
- (4) it will, despite modifications, even to a very large number, or all of the nucleosides, still have “RNA-like” properties, *i.e.*, it will possess the overall structural, chemical and physical properties of an RNA molecule, even though not exclusively, or even

partly, of ribonucleotide-based content. For example, an iRNA agent can contain, *e.g.*, a sense and/or an antisense strand in which all of the nucleotide sugars contain *e.g.*, 2' fluoro in place of 2' hydroxyl. This deoxyribonucleotide-containing agent can still be expected to exhibit RNA-like properties. While not wishing to be bound by theory, the electronegative fluorine prefers an axial orientation when attached to the C2' position of ribose. This spatial preference of fluorine can, in turn, force the sugars to adopt a C<sub>3'</sub>-*endo* pucker. This is the same puckering mode as observed in RNA molecules and gives rise to the RNA-characteristic A-family-type helix. Further, since fluorine is a good hydrogen bond acceptor, it can participate in the same hydrogen bonding interactions with water molecules that are known to stabilize RNA structures. (Generally, it is preferred that a modified moiety at the 2' sugar position will be able to enter into H-bonding which is more characteristic of the OH moiety of a ribonucleotide than the H moiety of a deoxyribonucleotide. A preferred iRNA agent will: exhibit a C<sub>3'</sub>-*endo* pucker in all, or at least 50, 75, 80, 85, 90, or 95 % of its sugars; exhibit a C<sub>3'</sub>-*endo* pucker in a sufficient amount of its sugars that it can give rise to the RNA-characteristic A-family-type helix; will have no more than 20, 10, 5, 4, 3, 2, or 1 sugar which is not a C<sub>3'</sub>-*endo* pucker structure. These limitations are particularly preferably in the antisense strand;

(5) regardless of the nature of the modification, and even though the RNA agent can contain deoxynucleotides or modified deoxynucleotides, particularly in overhang or other single strand regions, it is preferred that DNA molecules, or any molecule in which more than 50, 60, or 70 % of the nucleotides in the molecule, or more than 50, 60, or 70 % of the nucleotides in a duplexed region are deoxyribonucleotides, or modified deoxyribonucleotides which are deoxy at the 2' position, are excluded from the definition of RNA agent.

A "single strand iRNA agent" as used herein, is an iRNA agent which is made up of a single molecule. It may include a duplexed region, formed by intra-strand pairing, *e.g.*, it may be, or include, a hairpin or pan-handle structure. Single strand iRNA agents are preferably antisense with regard to the target molecule. In preferred embodiments single strand iRNA agents are 5' phosphorylated or include a phosphoryl analog at the 5' prime terminus. 5'-phosphate modifications include those which are compatible with RISC mediated gene silencing. Suitable modifications include: 5'-monophosphate ((HO)<sub>2</sub>(O)P-O-

5'); 5'-diphosphate ((HO)<sub>2</sub>(O)P-O-P(HO)(O)-O-5'); 5'-triphosphate ((HO)<sub>2</sub>(O)P-O-(HO)(O)P-O-P(HO)(O)-O-5'); 5'-guanosine cap (7-methylated or non-methylated) (7m-G-O-5'-(HO)(O)P-O-(HO)(O)P-O-P(HO)(O)-O-5'); 5'-adenosine cap (Appp), and any modified or unmodified nucleotide cap structure (N-O-5'-(HO)(O)P-O-(HO)(O)P-O-P(HO)(O)-O-5'); 5'-monothiophosphate (phosphorothioate; (HO)<sub>2</sub>(S)P-O-5'); 5'-monodithiophosphate (phosphorodithioate; (HO)(HS)(S)P-O-5'), 5'-phosphorothiolate ((HO)<sub>2</sub>(O)P-S-5'); any additional combination of oxygen/sulfur replaced monophosphate, diphosphate and triphosphates (*e.g.* 5'-alpha-thiotriphosphate, 5'-gamma-thiotriphosphate, etc.), 5'-phosphoramidates ((HO)<sub>2</sub>(O)P-NH-5', (HO)(NH<sub>2</sub>)(O)P-O-5'), 5'-alkylphosphonates (R=alkyl=methyl, ethyl, isopropyl, propyl, etc., *e.g.* RP(OH)(O)-O-5'-, (OH)<sub>2</sub>(O)P-5'-CH<sub>2</sub>-), 5'-alkyletherphosphonates (R=alkylether=methoxymethyl (MeOCH<sub>2</sub>-), ethoxymethyl, etc., *e.g.* RP(OH)(O)-O-5'-). (These modifications can also be used with the antisense strand of a double stranded iRNA.)

A single strand iRNA agent should be sufficiently long that it can enter the RISC and participate in RISC mediated cleavage of a target mRNA. A single strand iRNA agent is at least 14, and more preferably at least 15, 20, 25, 29, 35, 40, or 50 nucleotides in length. It is preferably less than 200, 100, or 60 nucleotides in length.

Hairpin iRNA agents will have a duplex region equal to or at least 17, 18, 19, 29, 21, 22, 23, 24, or 25 nucleotide pairs. The duplex region will preferably be equal to or less than 200, 100, or 50, in length. Preferred ranges for the duplex region are 15-30, 17 to 23, 19 to 23, and 19 to 21 nucleotides pairs in length. The hairpin will preferably have a single strand overhang or terminal unpaired region, preferably the 3', and preferably of the antisense side of the hairpin. Preferred overhangs are 2-3 nucleotides in length.

A "double stranded (ds) iRNA agent" as used herein, is an iRNA agent which includes more than one, and preferably two, strands in which interchain hybridization can form a region of duplex structure.

The antisense strand of a double stranded iRNA agent should be equal to or at least, 14, 15, 16, 17, 18, 19, 25, 29, 40, or 60 nucleotides in length. It should be equal to or less than 200, 100, or 50, nucleotides in length. Preferred ranges are 17 to 25, 19 to 23, and 19 to 21 nucleotides in length.

The sense strand of a double stranded iRNA agent should be equal to or at least 14, 15, 16 17, 18, 19, 25, 29, 40, or 60 nucleotides in length. It should be equal to or less than 200, 100, or 50, nucleotides in length. Preferred ranges are 17 to 25, 19 to 23, and 19 to 21 nucleotides in length.

5        The double strand portion of a double stranded iRNA agent should be equal to or at least, 14, 15, 16 17, 18, 19, 20, 21, 22, 23, 24, 25, 29, 40, or 60 nucleotide pairs in length. It should be equal to or less than 200, 100, or 50, nucleotides pairs in length. Preferred ranges are 15-30, 17 to 23, 19 to 23, and 19 to 21 nucleotides pairs in length.

10        In many embodiments, the ds iRNA agent is sufficiently large that it can be cleaved by an endogenous molecule, *e.g.*, by Dicer, to produce smaller ds iRNA agents, *e.g.*, sRNAs agents

15        It may be desirable to modify one or both of the antisense and sense strands of a double strand iRNA agent. In some cases they will have the same modification or the same class of modification but in other cases the sense and antisense strand will have different modifications, *e.g.*, in some cases it is desirable to modify only the sense strand. It may be desirable to modify only the sense strand, *e.g.*, to inactivate it, *e.g.*, the sense strand can be modified in order to inactivate the sense strand and prevent formation of an active sRNA/protein or RISC. This can be accomplished by a modification which prevents 5'-phosphorylation of the sense strand, *e.g.*, by modification with a 5'-O-methyl ribonucleotide (see Nykänen *et al.*, (2001) ATP requirements and small interfering RNA structure in the RNA interference pathway. Cell 107, 309-321.) Other modifications which prevent phosphorylation can also be used, *e.g.*, simply substituting the 5'-OH by H rather than O-Me. Alternatively, a large bulky group may be added to the 5'-phosphate turning it into a phosphodiester linkage, though this may be less desirable as phosphodiesterases can cleave  
25        such a linkage and release a functional sRNA 5'-end. Antisense strand modifications include 5' phosphorylation as well as any of the other 5' modifications discussed herein, particularly the 5' modifications discussed above in the section on single stranded iRNA molecules.

30        It is preferred that the sense and antisense strands be chosen such that the ds iRNA agent includes a single strand or unpaired region at one or both ends of the molecule. Thus, a ds iRNA agent contains sense and antisense strands, preferable paired to contain an overhang, *e.g.*, one or two 5' or 3' overhangs but preferably a 3' overhang of 2-3



nucleotides. Most embodiments will have a 3' overhang. Preferred sRNA agents will have single-stranded overhangs, preferably 3' overhangs, of 1 or preferably 2 or 3 nucleotides in length at each end. The overhangs can be the result of one strand being longer than the other, or the result of two strands of the same length being staggered. 5' ends are preferably phosphorylated.

Preferred lengths for the duplexed region is between 15 and 30, most preferably 18, 19, 20, 21, 22, and 23 nucleotides in length, *e.g.*, in the sRNA agent range discussed above. sRNA agents can resemble in length and structure the natural Dicer processed products from long dsRNAs. Embodiments in which the two strands of the sRNA agent are linked, *e.g.*, covalently linked are also included. Hairpin, or other single strand structures which provide the required double stranded region, and preferably a 3' overhang are also within the invention.

The isolated iRNA agents described herein, including ds iRNA agents and sRNA agents can mediate silencing of a target RNA, *e.g.*, mRNA, *e.g.*, a transcript of a gene that encodes a protein. For convenience, such mRNA is also referred to herein as mRNA to be silenced. Such a gene is also referred to as a target gene. In general, the RNA to be silenced is an endogenous gene or a pathogen gene. In addition, RNAs other than mRNA, *e.g.*, tRNAs, and viral RNAs, can also be targeted.

As used herein, the phrase "mediates RNAi" refers to the ability to silence, in a sequence specific manner, a target RNA. While not wishing to be bound by theory, it is believed that silencing uses the RNAi machinery or process and a guide RNA, *e.g.*, an sRNA agent of 21 to 23 nucleotides.

As used herein, "specifically hybridizable" and "complementary" are terms which are used to indicate a sufficient degree of complementarity such that stable and specific binding occurs between a compound of the invention and a target RNA molecule. Specific binding requires a sufficient degree of complementarity to avoid non-specific binding of the oligomeric compound to non-target sequences under conditions in which specific binding is desired, *i.e.*, under physiological conditions in the case of *in vivo* assays or therapeutic treatment, or in the case of *in vitro* assays, under conditions in which the assays are performed. The non-target sequences typically differ by at least 5 nucleotides.



In one embodiment, an iRNA agent is “sufficiently complementary” to a target RNA, *e.g.*, a target mRNA, such that the iRNA agent silences production of protein encoded by the target mRNA. In another embodiment, the iRNA agent is “exactly complementary” (excluding the RRMS containing subunit(s)) to a target RNA, *e.g.*, the target RNA and the  
5 iRNA agent anneal, preferably to form a hybrid made exclusively of Watson-Crick basepairs in the region of exact complementarity. A “sufficiently complementary” target RNA can include an internal region (*e.g.*, of at least 10 nucleotides) that is exactly complementary to a target RNA. Moreover, in some embodiments, the iRNA agent specifically discriminates a single-nucleotide difference. In this case, the iRNA agent only mediates RNAi if exact  
10 complementary is found in the region (*e.g.*, within 7 nucleotides of) the single-nucleotide difference.

As used herein, the term “oligonucleotide” refers to a nucleic acid molecule (RNA or DNA) preferably of length less than 100, 200, 300, or 400 nucleotides.

RNA agents discussed herein include otherwise unmodified RNA as well as RNA  
15 which have been modified, *e.g.*, to improve efficacy, and polymers of nucleoside surrogates. Unmodified RNA refers to a molecule in which the components of the nucleic acid, namely sugars, bases, and phosphate moieties, are the same or essentially the same as that which occur in nature, preferably as occur naturally in the human body. The art has referred to rare or unusual, but naturally occurring, RNAs as modified RNAs, see, *e.g.*, Limbach *et al.*,  
20 (1994) Summary: the modified nucleosides of RNA, *Nucleic Acids Res.* 22: 2183-2196. Such rare or unusual RNAs, often termed modified RNAs (apparently because they are typically the result of a post transcriptionally modification) are within the term unmodified RNA, as used herein. Modified RNA as used herein refers to a molecule in which one or more of the components of the nucleic acid, namely sugars, bases, and phosphate moieties,  
25 are different from that which occur in nature, preferably different from that which occurs in the human body. While they are referred to as modified “RNAs,” they will of course, because of the modification, include molecules which are not RNAs. Nucleoside surrogates are molecules in which the ribophosphate backbone is replaced with a non-ribophosphate construct that allows the bases to be presented in the correct spatial relationship such that  
30 hybridization is substantially similar to what is seen with a ribophosphate backbone, *e.g.*,

non-charged mimics of the ribophosphate backbone. Examples of all of the above are discussed herein.

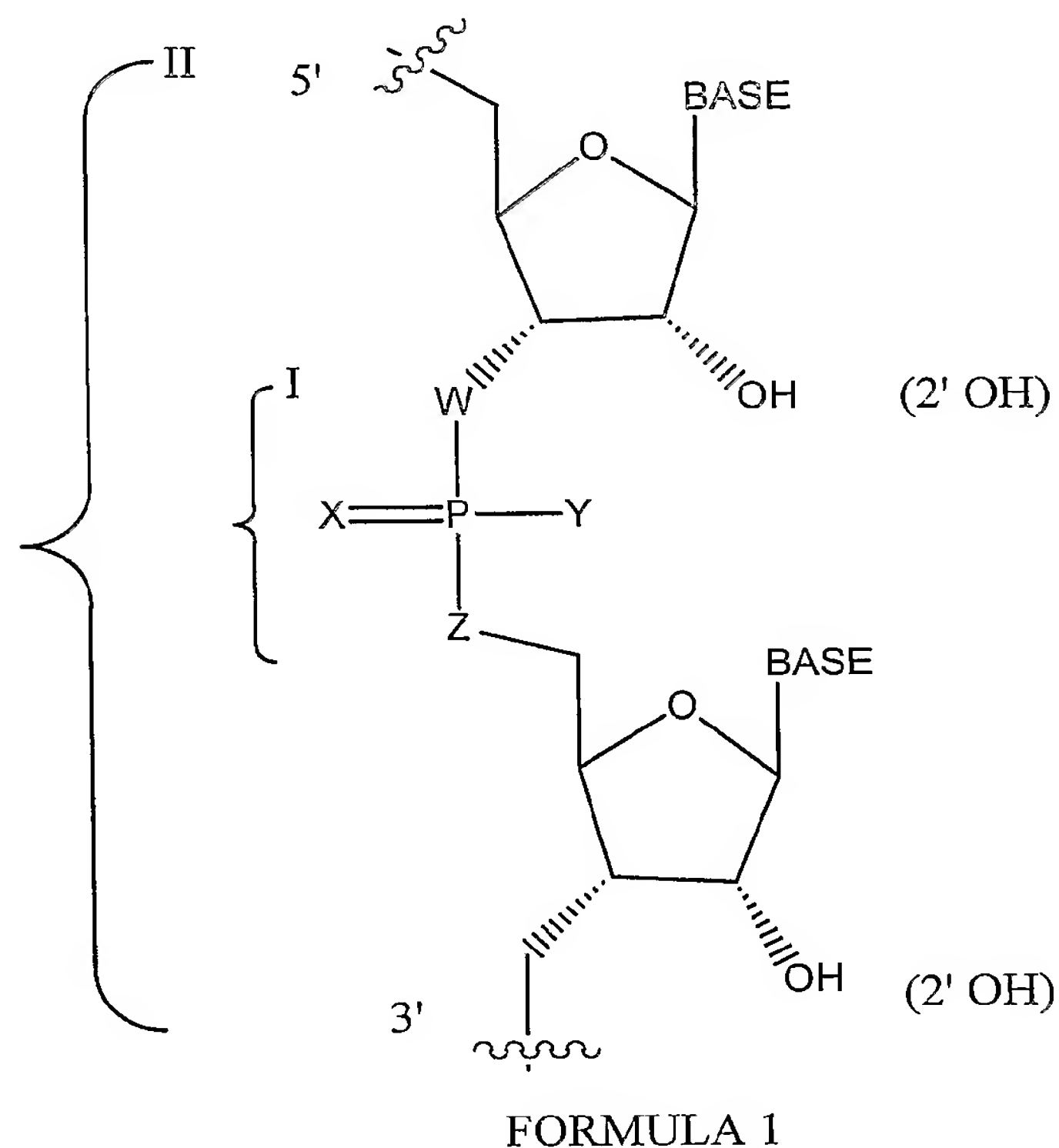
Much of the discussion below refers to single strand molecules. In many embodiments of the invention a double stranded iRNA agent, *e.g.*, a partially double stranded  
5 iRNA agent, is required or preferred. Thus, it is understood that that double stranded structures (*e.g.* where two separate molecules are contacted to form the double stranded region or where the double stranded region is formed by intramolecular pairing (*e.g.*, a hairpin structure)) made of the single stranded structures described below are within the invention. Preferred lengths are described elsewhere herein.

10 As nucleic acids are polymers of subunits or monomers, many of the modifications described below occur at a position which is repeated within a nucleic acid, *e.g.*, a modification of a base, or a phosphate moiety, or the a non-linking O of a phosphate moiety. In some cases the modification will occur at all of the subject positions in the nucleic acid but in many, and infact in most cases it will not. By way of example, a modification may only  
15 occur at a 3' or 5' terminal position, may only occur in a terminal regions, *e.g.* at a position on a terminal nucleotide or in the last 2, 3, 4, 5, or 10 nucleotides of a strand. A modification may occur in a double strand region, a single strand region, or in both. A modification may occur only in the double strand region of an RNA or may only occur in a single strand region of an RNA. *E.g.*, a phosphorothioate modification at a non-linking O position may only  
20 occur at one or both termini, may only occur in a terminal regions, *e.g.*, at a position on a terminal nucleotide or in the last 2, 3, 4, 5, or 10 nucleotides of a strand, or may occur in double strand and single strand regions, particularly at termini. The 5' end or ends can be phosphorylated.

In some embodiments it is particularly preferred, *e.g.*, to enhance stability, to include  
25 particular bases in overhangs, or to include modified nucleotides or nucleotide surrogates, in single strand overhangs, *e.g.*, in a 5' or 3' overhang, or in both. *E.g.*, it can be desirable to include purine nucleotides in overhangs. In some embodiments all or some of the bases in a 3' or 5' overhang will be modified, *e.g.*, with a modification described herein. Modifications can include, *e.g.*, the use of modifications at the 2' OH group of the ribose sugar, *e.g.*, the use  
30 of deoxyribonucleotides, *e.g.*, deoxythymidine, instead of ribonucleotides, and modifications

in the phosphate group, *e.g.*, phosphothioate modifications. Overhangs need not be homologous with the target sequence.

Modifications and nucleotide surrogates are discussed below.



5

The scaffold presented above in Formula 1 represents a portion of a ribonucleic acid. The basic components are the ribose sugar, the base, the terminal phosphates, and phosphate internucleotide linkers. Where the bases are naturally occurring bases, *e.g.*, adenine, uracil, guanine or cytosine, the sugars are the unmodified 2' hydroxyl ribose sugar (as depicted) and W, X, Y, and Z are all O, Formula 1 represents a naturally occurring unmodified oligoribonucleotide.

Unmodified oligoribonucleotides may be less than optimal in some applications, *e.g.*, unmodified oligoribonucleotides can be prone to degradation by *e.g.*, cellular nucleases. Nucleases can hydrolyze nucleic acid phosphodiester bonds. However, chemical

15

modifications to one or more of the above RNA components can confer improved properties, and, *e.g.*, can render oligoribonucleotides more stable to nucleases. Unmodified oligoribonucleotides may also be less than optimal in terms of offering tethering points for attaching ligands or other moieties to an iRNA agent.

5 Modified nucleic acids and nucleotide surrogates can include one or more of:

(i) alteration, *e.g.*, replacement, of one or both of the non-linking (X and Y) phosphate oxygens and/or of one or more of the linking (W and Z) phosphate oxygens (When the phosphate is in the terminal position, one of the positions W or Z will not link the phosphate to an additional element in a naturally occurring ribonucleic acid. However, for simplicity of terminology, except where otherwise noted, the W position at the 5' end of a nucleic acid and the terminal Z position at the 3' end of a nucleic acid, are within the term "linking phosphate oxygens" as used herein.);

(ii) alteration, *e.g.*, replacement, of a constituent of the ribose sugar, *e.g.*, of the 2' hydroxyl on the ribose sugar, or wholesale replacement of the ribose sugar with a structure other than ribose, *e.g.*, as described herein;

(iii) wholesale replacement of the phosphate moiety (bracket I) with "dephospho" linkers;

(iv) modification or replacement of a naturally occurring base;

(v) replacement or modification of the ribose-phosphate backbone (bracket II);

20 (vi) modification of the 3' end or 5' end of the RNA, *e.g.*, removal, modification or replacement of a terminal phosphate group or conjugation of a moiety, *e.g.* a fluorescently labeled moiety, to either the 3' or 5' end of RNA.

The terms replacement, modification, alteration, and the like, as used in this context, do not imply any process limitation, *e.g.*, modification does not mean that one must start with a reference or naturally occurring ribonucleic acid and modify it to produce a modified ribonucleic acid but rather modified simply indicates a difference from a naturally occurring molecule.

It is understood that the actual electronic structure of some chemical entities cannot be adequately represented by only one canonical form (*i.e.* Lewis structure). While not wishing to be bound by theory, the actual structure can instead be some hybrid or weighted average of two or more canonical forms, known collectively as resonance forms or

structures. Resonance structures are not discrete chemical entities and exist only on paper. They differ from one another only in the placement or "localization" of the bonding and nonbonding electrons for a particular chemical entity. It can be possible for one resonance structure to contribute to a greater extent to the hybrid than the others. Thus, the written and graphical descriptions of the embodiments of the present invention are made in terms of what the art recognizes as the predominant resonance form for a particular species. For example, any phosphoroamidate (replacement of a nonlinking oxygen with nitrogen) would be represented by  $X = O$  and  $Y = N$  in the above figure.

Specific modifications are discussed in more detail below.

#### 10        The Phosphate Group

The phosphate group is a negatively charged species. The charge is distributed equally over the two non-linking oxygen atoms (*i.e.*, X and Y in Formula 1 above). However, the phosphate group can be modified by replacing one of the oxygens with a different substituent. One result of this modification to RNA phosphate backbones can be increased resistance of the oligoribonucleotide to nucleolytic breakdown. Thus while not wishing to be bound by theory, it can be desirable in some embodiments to introduce alterations which result in either an uncharged linker or a charged linker with unsymmetrical charge distribution.

Examples of modified phosphate groups include phosphorothioate, phosphoroselenates, borano phosphates, borano phosphate esters, hydrogen phosphonates, phosphoroamidates, alkyl or aryl phosphonates and phosphotriesters. Phosphorodithioates have both non-linking oxygens replaced by sulfur. Unlike the situation where only one of X or Y is altered, the phosphorus center in the phosphorodithioates is achiral which precludes the formation of oligoribonucleotides diastereomers. Diastereomer formation can result in a preparation in which the individual diastereomers exhibit varying resistance to nucleases. Further, the hybridization affinity of RNA containing chiral phosphate groups can be lower relative to the corresponding unmodified RNA species. Thus, while not wishing to be bound by theory, modifications to both X and Y which eliminate the chiral center, *e.g.* phosphorodithioate formation, may be desirable in that they cannot produce diastereomer mixtures. Thus, X can be any one of S, Se, B, C, H, N, or OR (R is alkyl or aryl). Thus Y



can be any one of S, Se, B, C, H, N, or OR (R is alkyl or aryl). Replacement of X and/or Y with sulfur is preferred.

The phosphate linker can also be modified by replacement of a linking oxygen (*i.e.*, W or Z in Formula 1) with nitrogen (bridged phosphoroamidates), sulfur (bridged phosphorothioates) and carbon (bridged methylenephosphonates). The replacement can occur at a terminal oxygen (position W (3') or position Z (5')). Replacement of W with carbon or Z with nitrogen is preferred.

Candidate agents can be evaluated for suitability as described below.

#### The Sugar Group

A modified RNA can include modification of all or some of the sugar groups of the ribonucleic acid. *E.g.*, the 2' hydroxyl group (OH) can be modified or replaced with a number of different "oxy" or "deoxy" substituents. While not being bound by theory, enhanced stability is expected since the hydroxyl can no longer be deprotonated to form a 2' alkoxide ion. The 2' alkoxide can catalyze degradation by intramolecular nucleophilic attack on the linker phosphorus atom. Again, while not wishing to be bound by theory, it can be desirable to some embodiments to introduce alterations in which alkoxide formation at the 2' position is not possible.

Examples of "oxy"-2' hydroxyl group modifications include alkoxy or aryloxy (OR, *e.g.*, R = H, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl or sugar); polyethyleneglycols (PEG),  $O(CH_2CH_2O)_nCH_2CH_2OR$ ; "locked" nucleic acids (LNA) in which the 2' hydroxyl is connected, *e.g.*, by a methylene bridge, to the 4' carbon of the same ribose sugar; O-AMINE (AMINE =  $NH_2$ ; alkylamino, dialkylamino, heterocyclyl, arylamino, diaryl amino, heteroaryl amino, or diheteroaryl amino, ethylene diamine, polyamino) and aminoalkoxy,  $O(CH_2)_nAMINE$ , (*e.g.*, AMINE =  $NH_2$ ; alkylamino, dialkylamino, heterocyclyl, arylamino, diaryl amino, heteroaryl amino, or diheteroaryl amino, ethylene diamine, polyamino). It is noteworthy that oligonucleotides containing only the methoxyethyl group (MOE),  $(OCH_2CH_2OCH_3)$ , a PEG derivative, exhibit nuclease stabilities comparable to those modified with the robust phosphorothioate modification.

"Deoxy" modifications include hydrogen (*i.e.* deoxyribose sugars, which are of particular relevance to the overhang portions of partially ds RNA); halo (*e.g.*, fluoro); amino

(*e.g.* NH<sub>2</sub>; alkylamino, dialkylamino, heterocyclyl, arylamino, diaryl amino, heteroaryl amino, diheteroaryl amino, or amino acid); NH(CH<sub>2</sub>CH<sub>2</sub>NH)<sub>n</sub>CH<sub>2</sub>CH<sub>2</sub>-AMINE (AMINE = NH<sub>2</sub>; alkylamino, dialkylamino, heterocyclyl, arylamino, diaryl amino, heteroaryl amino, or diheteroaryl amino), -NHC(O)R (R = alkyl, cycloalkyl, aryl, aralkyl, heteroaryl or sugar),  
5 cyano; mercapto; alkyl-thio-alkyl; thioalkoxy; and alkyl, cycloalkyl, aryl, alkenyl and alkynyl, which may be optionally substituted with *e.g.*, an amino functionality. Preferred substituents are 2'-methoxyethyl, 2'-OCH<sub>3</sub>, 2'-O-allyl, 2'-C- allyl, and 2'-fluoro.

The sugar group can also contain one or more carbons that possess the opposite stereochemical configuration than that of the corresponding carbon in ribose. Thus, a  
10 modified RNA can include nucleotides containing *e.g.*, arabinose, as the sugar.

Modified RNA's can also include "abasic" sugars, which lack a nucleobase at C-1'. These abasic sugars can also be further contain modifications at one or more of the constituent sugar atoms.

To maximize nuclease resistance, the 2' modifications can be used in combination  
15 with one or more phosphate linker modifications (*e.g.*, phosphorothioate). The so-called "chimeric" oligonucleotides are those that contain two or more different modifications.

The modification can also entail the wholesale replacement of a ribose structure with another entity at one or more sites in the iRNA agent. These modifications are described in section entitled Ribose Replacements for RRMSs.

20 Candidate modifications can be evaluated as described below.

#### Replacement of the Phosphate Group

The phosphate group can be replaced by non-phosphorus containing connectors (*cf.* Bracket I in Formula 1 above). While not wishing to be bound by theory, it is believed that since the charged phosphodiester group is the reaction center in nucleolytic degradation, its  
25 replacement with neutral structural mimics should impart enhanced nuclease stability. Again, while not wishing to be bound by theory, it can be desirable, in some embodiment, to introduce alterations in which the charged phosphate group is replaced by a neutral moiety.

Examples of moieties which can replace the phosphate group include siloxane, carbonate, carboxymethyl, carbamate, amide, thioether, ethylene oxide linker, sulfonate,  
30 sulfonamide, thioformacetal, formacetal, oxime, methyleneimino, methylenemethylimino,

methylenehydrazo, methylenedimethylhydrazo and methyleneoxymethylimino. Preferred replacements include the methylenecarbonylamino and methylenemethylimino groups.

Candidate modifications can be evaluated as described below.

#### Replacement of Ribophosphate Backbone

5 Oligonucleotide- mimicking scaffolds can also be constructed wherein the phosphate linker and ribose sugar are replaced by nuclease resistant nucleoside or nucleotide surrogates (see Bracket II of Formula 1 above). While not wishing to be bound by theory, it is believed that the absence of a repetitively charged backbone diminishes binding to proteins that recognize polyanions (*e.g.* nucleases). Again, while not wishing to be bound by theory, it  
10 can be desirable in some embodiment, to introduce alterations in which the bases are tethered by a neutral surrogate backbone.

Examples include the morpholino, cyclobutyl, pyrrolidine and peptide nucleic acid (PNA) nucleoside surrogates. A preferred surrogate is a PNA surrogate.

Candidate modifications can be evaluated as described below.

#### Terminal Modifications

15 The 3' and 5' ends of an oligonucleotide can be modified. Such modifications can be at the 3' end, 5' end or both ends of the molecule. They can include modification or replacement of an entire terminal phosphate or of one or more of the atoms of the phosphate group. *E.g.*, the 3' and 5' ends of an oligonucleotide can be conjugated to other functional  
20 molecular entities such as labeling moieties, *e.g.*, fluorophores (*e.g.*, pyrene, TAMRA, fluorescein, Cy3 or Cy5 dyes) or protecting groups (based *e.g.*, on sulfur, silicon, boron or ester). The functional molecular entities can be attached to the sugar through a phosphate group and/or a spacer. The terminal atom of the spacer can connect to or replace the linking atom of the phosphate group or the C-3' or C-5' O, N, S or C group of the sugar.

25 Alternatively, the spacer can connect to or replace the terminal atom of a nucleotide surrogate (*e.g.*, PNAs). These spacers or linkers can include *e.g.*,  $-(CH_2)_n-$ ,  $-(CH_2)_nN-$ ,  $-(CH_2)_nO-$ ,  $-(CH_2)_nS-$ ,  $O(CH_2CH_2O)_nCH_2CH_2OH$  (*e.g.*,  $n = 3$  or  $6$ ), abasic sugars, amide, carboxy, amine, oxyamine, oxyimine, thioether, disulfide, thiourea, sulfonamide, or morpholino, or biotin and fluorescein reagents. When a spacer/phosphate-functional  
30 molecular entity-spacer/phosphate array is interposed between two strands of iRNA agents,

this array can substitute for a hairpin RNA loop in a hairpin-type RNA agent. The 3' end can be an -OH group. While not wishing to be bound by theory, it is believed that conjugation of certain moieties can improve transport, hybridization, and specificity properties. Again, while not wishing to be bound by theory, it may be desirable to introduce terminal alterations that improve nuclease resistance. Other examples of terminal modifications include dyes, intercalating agents (*e.g.* acridines), cross-linkers (*e.g.* psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (*e.g.*, phenazine, dihydrophenazine), artificial endonucleases (*e.g.* EDTA), lipophilic carriers (*e.g.*, cholesterol, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine) and peptide conjugates (*e.g.*, antennapedia peptide, Tat peptide), alkylating agents, phosphate, amino, mercapto, PEG (*e.g.*, PEG-40K), MPEG, [MPEG]<sub>2</sub>, polyamino, alkyl, substituted alkyl, radiolabeled markers, enzymes, haptens (*e.g.* biotin), transport/absorption facilitators (*e.g.*, aspirin, vitamin E, folic acid), synthetic ribonucleases (*e.g.*, imidazole, bisimidazole, histamine, imidazole clusters, acridine-imidazole conjugates, Eu<sup>3+</sup> complexes of tetraazamacrocycles).

Terminal modifications can be added for a number of reasons, including as discussed elsewhere herein to modulate activity or to modulate resistance to degradation. Terminal modifications useful for modulating activity include modification of the 5' end with phosphate or phosphate analogs. *E.g.*, in preferred embodiments iRNA agents, especially antisense strands, are 5' phosphorylated or include a phosphoryl analog at the 5' prime terminus. 5'-phosphate modifications include those which are compatible with RISC mediated gene silencing. Suitable modifications include: 5'-monophosphate ((HO)<sub>2</sub>(O)P-O-5'); 5'-diphosphate ((HO)<sub>2</sub>(O)P-O-P(HO)(O)-O-5'); 5'-triphosphate ((HO)<sub>2</sub>(O)P-O-(HO)(O)P-O-P(HO)(O)-O-5'); 5'-guanosine cap (7-methylated or non-methylated) (7m-G-O-5'-(HO)(O)P-O-(HO)(O)P-O-P(HO)(O)-O-5'); 5'-adenosine cap (Appp), and any modified or unmodified nucleotide cap structure (N-O-5'-(HO)(O)P-O-(HO)(O)P-O-P(HO)(O)-O-5'); 5'-monothiophosphate (phosphorothioate; (HO)<sub>2</sub>(S)P-O-5'); 5'-monodithiophosphate (phosphorodithioate; (HO)(HS)(S)P-O-5'), 5'-phosphorothiolate ((HO)<sub>2</sub>(O)P-S-5'); any additional combination of oxygen/sulfur replaced monophosphate, diphosphate and



triphosphates (*e.g.* 5'-alpha-thiotriphosphate, 5'-gamma-thiotriphosphate, etc.), 5'-phosphoramidates ((HO)<sub>2</sub>(O)P-NH-5', (HO)(NH<sub>2</sub>)(O)P-O-5'), 5'-alkylphosphonates (R=alkyl=methyl, ethyl, isopropyl, propyl, etc., *e.g.* RP(OH)(O)-O-5', (OH)<sub>2</sub>(O)P-5'-CH<sub>2</sub>-), 5'-alkyletherphosphonates (R=alkylether=methoxymethyl (MeOCH<sub>2</sub>-), ethoxymethyl, etc., *e.g.* RP(OH)(O)-O-5'-).

Terminal modifications useful for increasing resistance to degradation include

Terminal modifications can also be useful for monitoring distribution, and in such cases the preferred groups to be added include fluorophores, *e.g.*, fluorescein or an Alexa dye, *e.g.*, Alexa 488. Terminal modifications can also be useful for enhancing uptake, useful modifications for this include cholesterol. Terminal modifications can also be useful for cross-linking an RNA agent to another moiety; modifications useful for this include mitomycin C.

Candidate modifications can be evaluated as described below.

### The Bases

Adenine, guanine, cytosine and uracil are the most common bases found in RNA. These bases can be modified or replaced to provide RNA's having improved properties. *E.g.*, nuclease resistant oligoribonucleotides can be prepared with these bases or with synthetic and natural nucleobases (*e.g.*, inosine, thymine, xanthine, hypoxanthine, nubularine, isoguanisine, or tubercidine) and any one of the above modifications. Alternatively, substituted or modified analogs of any of the above bases, *e.g.*, "unusual bases" and "universal bases," can be employed. Examples include without limitation 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 5-halouracil, 5-(2-aminopropyl)uracil, 5-amino allyl uracil, 8-halo, amino, thiol, thioalkyl, hydroxyl and other 8-substituted adenines and guanines, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine, 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine, dihydrouracil, 3-deaza-5-azacytosine, 2-aminopurine, 5-alkyluracil, 7-alkylguanine, 5-alkyl cytosine, 7-deazaadenine, N6, N6-dimethyladenine, 2,6-diaminopurine, 5-amino-allyl-uracil, N3-methyluracil, substituted



1,2,4-triazoles, 2-pyridinone, 5-nitroindole, 3-nitropyrrole, 5-methoxyuracil, uracil-5-oxyacetic acid, 5-methoxycarbonylmethyluracil, 5-methyl-2-thiouracil, 5-methoxycarbonylmethyl-2-thiouracil, 5-methylaminomethyl-2-thiouracil, 3-(3-amino-3carboxypropyl)uracil, 3-methylcytosine, 5-methylcytosine, N<sup>4</sup>-acetyl cytosine, 2-thiocytosine, N6-methyladenine, N6-isopentyladenine, 2-methylthio-N6-isopentenyladenine, N-methylguanines, or O-alkylated bases. Further purines and pyrimidines include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in the Concise Encyclopedia Of Polymer Science And Engineering, pages 858-859, Kroschwitz, J. I., ed. John Wiley & Sons, 1990, and those disclosed by Englisch *et al.*, Angewandte Chemie, International Edition, 1991, 30, 613.

Generally, base changes are less preferred for promoting stability, but they can be useful for other reasons, *e.g.*, some, *e.g.*, 2,6-diaminopurine and 2 amino purine, are fluorescent. Modified bases can reduce target specificity. This should be taken into consideration in the design of iRNA agents.

Candidate modifications can be evaluated as described below.

#### Evaluation of Candidate RNA's

One can evaluate a candidate RNA agent, *e.g.*, a modified RNA, for a selected property by exposing the agent or modified molecule and a control molecule to the appropriate conditions and evaluating for the presence of the selected property. For example, resistance to a degradant can be evaluated as follows. A candidate modified RNA (and preferably a control molecule, usually the unmodified form) can be exposed to degradative conditions, *e.g.*, exposed to a milieu, which includes a degradative agent, *e.g.*, a nuclease. *E.g.*, one can use a biological sample, *e.g.*, one that is similar to a milieu, which might be encountered, in therapeutic use, *e.g.*, blood or a cellular fraction, *e.g.*, a cell-free homogenate or disrupted cells. The candidate and control could then be evaluated for resistance to degradation by any of a number of approaches. For example, the candidate and control could be labeled, preferably prior to exposure, with, *e.g.*, a radioactive or enzymatic label, or a fluorescent label, such as Cy3 or Cy5. Control and modified RNA's can be incubated with the degradative agent, and optionally a control, *e.g.*, an inactivated, *e.g.*, heat inactivated, degradative agent. A physical parameter, *e.g.*, size, of the modified and control molecules

are then determined. They can be determined by a physical method, *e.g.*, by polyacrylamide gel electrophoresis or a sizing column, to assess whether the molecule has maintained its original length, or assessed functionally. Alternatively, Northern blot analysis can be used to assay the length of an unlabeled modified molecule.

5           A functional assay can also be used to evaluate the candidate agent. A functional assay can be applied initially or after an earlier non-functional assay, (*e.g.*, assay for resistance to degradation) to determine if the modification alters the ability of the molecule to silence gene expression. For example, a cell, *e.g.*, a mammalian cell, such as a mouse or human cell, can be co-transfected with a plasmid expressing a fluorescent protein, *e.g.*, GFP,  
10   and a candidate RNA agent homologous to the transcript encoding the fluorescent protein (see, *e.g.*, WO 00/44914). For example, a modified dsRNA homologous to the GFP mRNA can be assayed for the ability to inhibit GFP expression by monitoring for a decrease in cell fluorescence, as compared to a control cell, in which the transfection did not include the candidate dsRNA, *e.g.*, controls with no agent added and/or controls with a non-modified  
15   RNA added. Efficacy of the candidate agent on gene expression can be assessed by comparing cell fluorescence in the presence of the modified and unmodified dsRNA agents.

          In an alternative functional assay, a candidate dsRNA agent homologous to an endogenous mouse gene, preferably a maternally expressed gene, such as *c-mos*, can be injected into an immature mouse oocyte to assess the ability of the agent to inhibit gene  
20   expression *in vivo* (see, *e.g.*, WO 01/36646). A phenotype of the oocyte, *e.g.*, the ability to maintain arrest in metaphase II, can be monitored as an indicator that the agent is inhibiting expression. For example, cleavage of *c-mos* mRNA by a dsRNA agent would cause the oocyte to exit metaphase arrest and initiate parthenogenetic development (Colledge *et al.* Nature 370: 65-68, 1994; Hashimoto *et al.* Nature, 370:68-71, 1994). The effect of the  
25   modified agent on target RNA levels can be verified by Northern blot to assay for a decrease in the level of target mRNA, or by Western blot to assay for a decrease in the level of target protein, as compared to a negative control. Controls can include cells in which with no agent is added and/or cells in which a non-modified RNA is added.

## References

### General References

The oligoribonucleotides and oligoribonucleosides used in accordance with this invention may be with solid phase synthesis, see for example "Oligonucleotide synthesis, a practical approach", Ed. M. J. Gait, IRL Press, 1984; "Oligonucleotides and Analogues, A  
5 Practical Approach", Ed. F. Eckstein, IRL Press, 1991 (especially Chapter 1, Modern machine-aided methods of oligodeoxyribonucleotide synthesis, Chapter 2, Oligoribonucleotide synthesis, Chapter 3, 2'-O--Methyloligoribonucleotide- s: synthesis and applications, Chapter 4, Phosphorothioate oligonucleotides, Chapter 5, Synthesis of  
10 oligonucleotide phosphorodithioates, Chapter 6, Synthesis of oligo-2'-deoxyribonucleoside methylphosphonates, and. Chapter 7, Oligodeoxynucleotides containing modified bases. Other particularly useful synthetic procedures, reagents, blocking groups and reaction conditions are described in Martin, P., *Helv. Chim. Acta*, **1995**, 78, 486-504; Beaucage, S. L. and Iyer, R. P., *Tetrahedron*, **1992**, 48, 2223-2311 and Beaucage, S. L. and Iyer, R. P.,  
15 *Tetrahedron*, **1993**, 49, 6123-6194, or references referred to therein.

Modification described in WO 00/44895, WO01/75164, or WO02/44321 can be used herein.

The disclosure of all publications, patents, and published patent applications listed herein are hereby incorporated by reference.

### Phosphate Group References

The preparation of phosphinate oligoribonucleotides is described in U.S. Pat. No. 5,508,270. The preparation of alkyl phosphonate oligoribonucleotides is described in U.S. Pat. No. 4,469,863. The preparation of phosphoramidite oligoribonucleotides is described in U.S. Pat. No. 5,256,775 or U.S. Pat. No. 5,366,878. The preparation of phosphotriester  
25 oligoribonucleotides is described in U.S. Pat. No. 5,023,243. The preparation of borano phosphate oligoribonucleotide is described in U.S. Pat. Nos. 5,130,302 and 5,177,198. The preparation of 3'-Deoxy-3'-amino phosphoramidate oligoribonucleotides is described in U.S. Pat. No. 5,476,925. 3'-Deoxy-3'-methylenephosphonate oligoribonucleotides is described in An, H, *et al. J. Org. Chem.* **2001**, 66, 2789-2801. Preparation of sulfur bridged nucleotides is

described in Sproat *et al. Nucleosides Nucleotides* **1988**, 7,651 and Crosstick *et al. Tetrahedron Lett.* **1989**, 30, 4693.

#### Sugar Group References

5        Modifications to the 2' modifications can be found in Verma, S. *et al. Annu. Rev. Biochem.* **1998**, 67, 99-134 and all references therein. Specific modifications to the ribose can be found in the following references: 2'-fluoro (Kawasaki *et al.*, *J. Med. Chem.*, **1993**, 36, 831-841), 2'-MOE (Martin, P. *Helv. Chim. Acta* **1996**, 79, 1930-1938), "LNA" (Wengel, *J. Acc. Chem. Res.* **1999**, 32, 301-310).

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#### Replacement of the Phosphate Group References

Methylenemethylimino linked oligoribonucleosides, also identified herein as MMI linked oligoribonucleosides, methylenedimethylhydrazo linked oligoribonucleosides, also identified herein as MDH linked oligoribonucleosides, and methylenecarbonylamino linked  
15    oligonucleosides, also identified herein as amide-3 linked oligoribonucleosides, and methyleneaminocarbonyl linked oligonucleosides, also identified herein as amide-4 linked oligoribonucleosides as well as mixed backbone compounds having, as for instance, alternating MMI and PO or PS linkages can be prepared as is described in U.S. Pat. Nos. 5,378,825, 5,386,023, 5,489,677 and in published PCT applications PCT/US92/04294 and  
20    PCT/US92/04305 (published as WO 92/20822 WO and 92/20823, respectively). Formacetal and thioformacetal linked oligoribonucleosides can be prepared as is described in U.S. Pat. Nos. 5,264,562 and 5,264,564. Ethylene oxide linked oligoribonucleosides can be prepared as is described in U.S. Pat. No. 5,223,618. Siloxane replacements are described in Cormier, J.F. *et al. Nucleic Acids Res.* **1988**, 16, 4583. Carbonate replacements are described  
25    in Tittensor, J.R. *J. Chem. Soc. C* **1971**, 1933. Carboxymethyl replacements are described in Edge, M.D. *et al. J. Chem. Soc. Perkin Trans. 1* **1972**, 1991. Carbamate replacements are described in Stirchak, E.P. *Nucleic Acids Res.* **1989**, 17, 6129.

#### Replacement of the Phosphate-Ribose Backbone References

30        Cyclobutyl sugar surrogate compounds can be prepared as is described in U.S. Pat. No. 5,359,044. Pyrrolidine sugar surrogate can be prepared as is described in U.S. Pat. No.

5,519,134. Morpholino sugar surrogates can be prepared as is described in U.S. Pat. Nos. 5,142,047 and 5,235,033, and other related patent disclosures. Peptide Nucleic Acids (PNAs) are known per se and can be prepared in accordance with any of the various procedures referred to in Peptide Nucleic Acids (PNA): Synthesis, Properties and Potential Applications, Bioorganic & Medicinal Chemistry, 1996, 4, 5-23. They may also be prepared in accordance with U.S. Pat. No. 5,539,083.

#### Terminal Modification References

Terminal modifications are described in Manoharan, M. *et al. Antisense and Nucleic Acid Drug Development 12*, 103-128 (2002) and references therein.

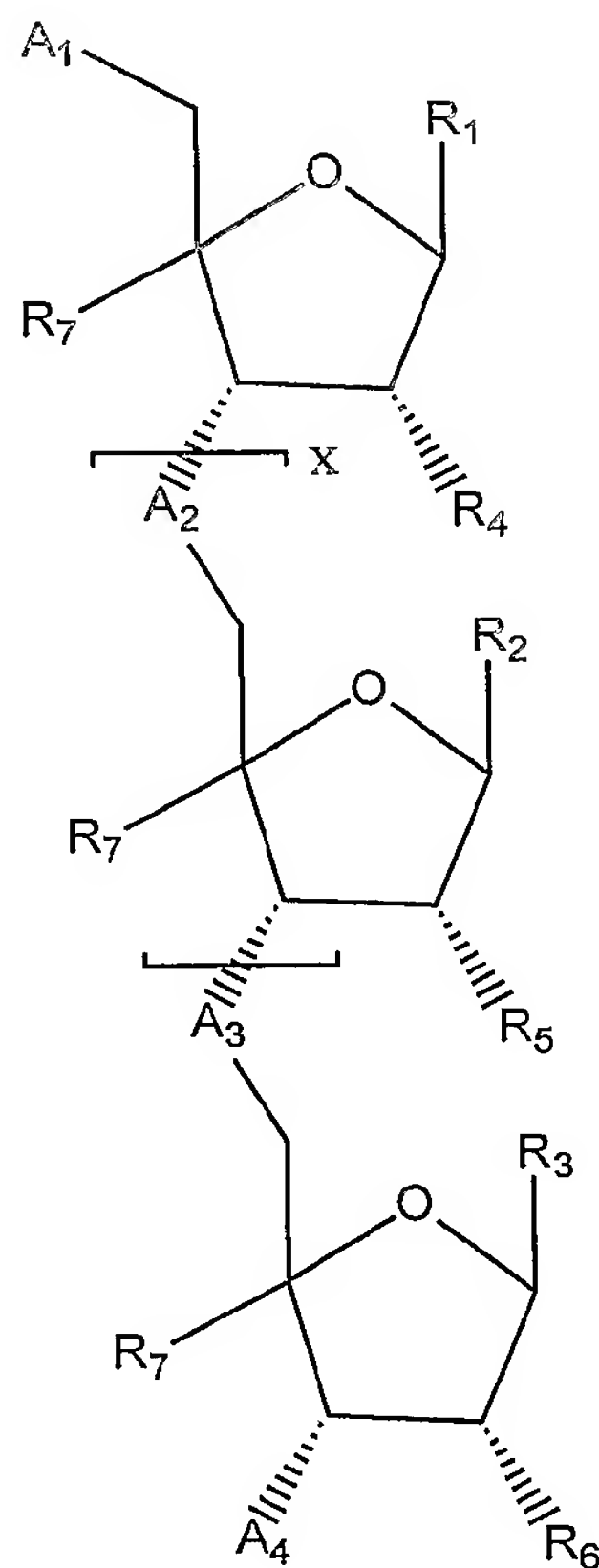
#### Bases References

N-2 substituted purine nucleoside amidites can be prepared as is described in U.S. Pat. No. 5,459,255. 3-Deaza purine nucleoside amidites can be prepared as is described in U.S. Pat. No. 5,457,191. 5,6-Substituted pyrimidine nucleoside amidites can be prepared as is described in U.S. Pat. No. 5,614,617. 5-Propynyl pyrimidine nucleoside amidites can be prepared as is described in U.S. Pat. No. 5,484,908. Additional references can be disclosed in the above section on base modifications.



Preferred iRNA Agents

Preferred RNA agents have the following structure (see Formula 2 below):



5

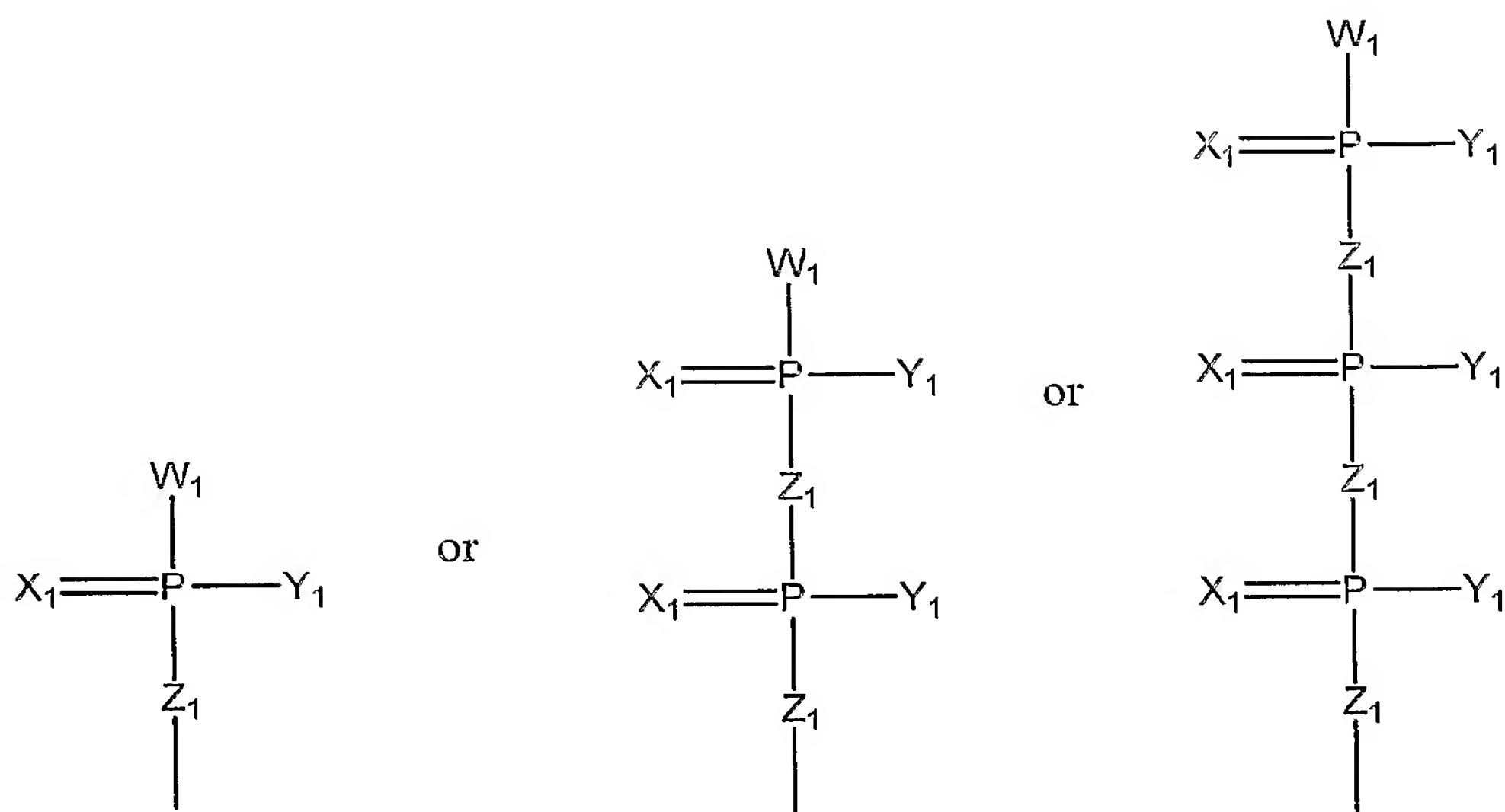
FORMULA 2

Referring to Formula 2 above,  $R^1$ ,  $R^2$ , and  $R^3$  are each, independently, H, (*i.e.* abasic nucleotides), adenine, guanine, cytosine and uracil, inosine, thymine, xanthine, hypoxanthine, nubularine, tubercidine, isoguanisine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 5-halouracil, 5-(2-aminopropyl)uracil, 5-amino allyl uracil, 8-halo, amino, thiol, thioalkyl, hydroxyl and other 8-substituted adenines and

guanines, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine,  
 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines,  
 including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine, dihydrouracil, 3-  
 deaza-5-azacytosine, 2-aminopurine, 5-alkyluracil, 7-alkylguanine, 5-alkyl cytosine, 7-  
 5 deazaadenine, 7-deazaguanine, N6, N6-dimethyladenine, 2,6-diaminopurine, 5-amino-allyl-  
 uracil, N3-methyluracil, substituted 1,2,4-triazoles, 2-pyridinone, 5-nitroindole, 3-  
 nitropyrrole, 5-methoxyuracil, uracil-5-oxyacetic acid, 5-methoxycarbonylmethyluracil, 5-  
 methyl-2-thiouracil, 5-methoxycarbonylmethyl-2-thiouracil, 5-methylaminomethyl-2-  
 thiouracil, 3-(3-amino-3carboxypropyl)uracil, 3-methylcytosine, 5-methylcytosine, N<sup>4</sup>-acetyl  
 10 cytosine, 2-thiocytosine, N6-methyladenine, N6-isopentyladenine, 2-methylthio-N6-  
 isopentenyladenine, N-methylguanines, or O-alkylated bases.

$R^4$ ,  $R^5$ , and  $R^6$  are each, independently,  $OR^8$ ,  $O(CH_2CH_2O)_mCH_2CH_2OR^8$ ;  
 $O(CH_2)_nR^9$ ;  $O(CH_2)_nOR^9$ , H; halo;  $NH_2$ ;  $NHR^8$ ;  $N(R^8)_2$ ;  $NH(CH_2CH_2NH)_mCH_2CH_2NHR^9$ ;  
 $NHC(O)R^8$ ; ; cyano; mercapto,  $SR^8$ ; alkyl-thio-alkyl; alkyl, aralkyl, cycloalkyl, aryl,  
 15 heteroaryl, alkenyl, alkynyl, each of which may be optionally substituted with halo, hydroxy,  
 oxo, nitro, haloalkyl, alkyl, alkaryl, aryl, aralkyl, alkoxy, aryloxy, amino, alkylamino,  
 dialkylamino, heterocyclyl, arylamino, diaryl amino, heteroaryl amino, diheteroaryl amino,  
 acylamino, alkylcarbonyl, arylcarbonyl, aminoalkyl, alkoxyalkyl, carboxy,  
 hydroxyalkyl, alkanesulfonyl, alkanesulfonamido, arenesulfonamido, aralkylsulfonamido,  
 20 alkylcarbonyl, acyloxy, cyano, or ureido; or  $R^4$ ,  $R^5$ , or  $R^6$  together combine with  $R^7$  to form  
 an [-O-CH<sub>2</sub>-] covalently bound bridge between the sugar 2' and 4' carbons.

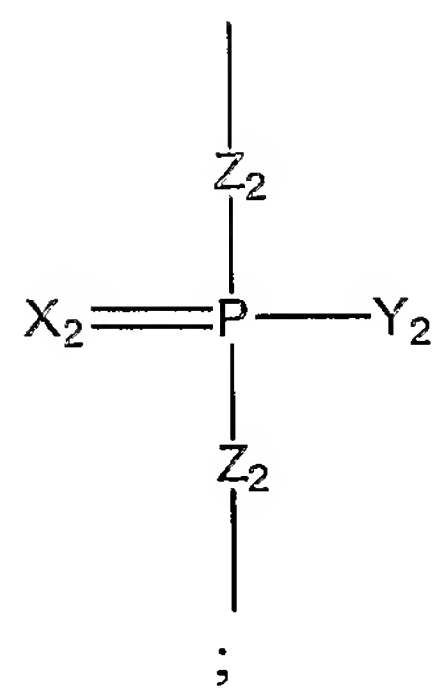
A<sup>1</sup> is:



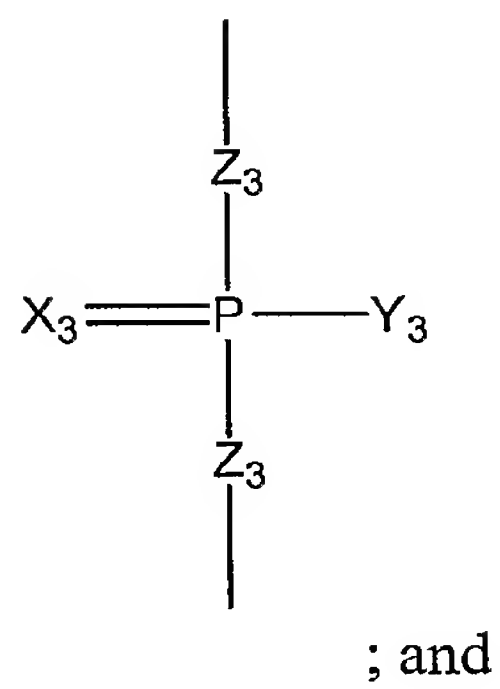
5 ; H; OH; OCH<sub>3</sub>; W<sup>1</sup>; an abasic nucleotide; or absent;

(a preferred A<sup>1</sup>, especially with regard to anti-sense strands, is chosen from 5'-monophosphate ((HO)<sub>2</sub>(O)P-O-5'), 5'-diphosphate ((HO)<sub>2</sub>(O)P-O-P(HO)(O)-O-5'), 5'-triphosphate ((HO)<sub>2</sub>(O)P-O-(HO)(O)P-O-P(HO)(O)-O-5'), 5'-guanosine cap (7-methylated or non-methylated) (7m-G-O-5'-(HO)(O)P-O-(HO)(O)P-O-P(HO)(O)-O-5'), 5'-adenosine cap (Appp), and any modified or unmodified nucleotide cap structure (N-O-5'-(HO)(O)P-O-(HO)(O)P-O-P(HO)(O)-O-5'), 5'-monothiophosphate (phosphorothioate; (HO)<sub>2</sub>(S)P-O-5'), 5'-monodithiophosphate (phosphorodithioate; (HO)(HS)(S)P-O-5'), 5'-phosphorothiolate ((HO)<sub>2</sub>(O)P-S-5'); any additional combination of oxygen/sulfur replaced monophosphate, diphosphate and triphosphates (*e.g.* 5'-alpha-thiotriphosphate, 5'-gamma-thiotriphosphate, etc.), 5'-phosphoramidates ((HO)<sub>2</sub>(O)P-NH-5', (HO)(NH<sub>2</sub>)(O)P-O-5'), 5'-alkylphosphonates (R=alkyl=methyl, ethyl, isopropyl, propyl, etc., *e.g.* RP(OH)(O)-O-5'-, (OH)<sub>2</sub>(O)P-5'-CH<sub>2</sub>-), 5'-alkyletherphosphonates (R=alkylether=methoxymethyl (MeOCH<sub>2</sub>-), ethoxymethyl, etc., *e.g.* RP(OH)(O)-O-5'-)).

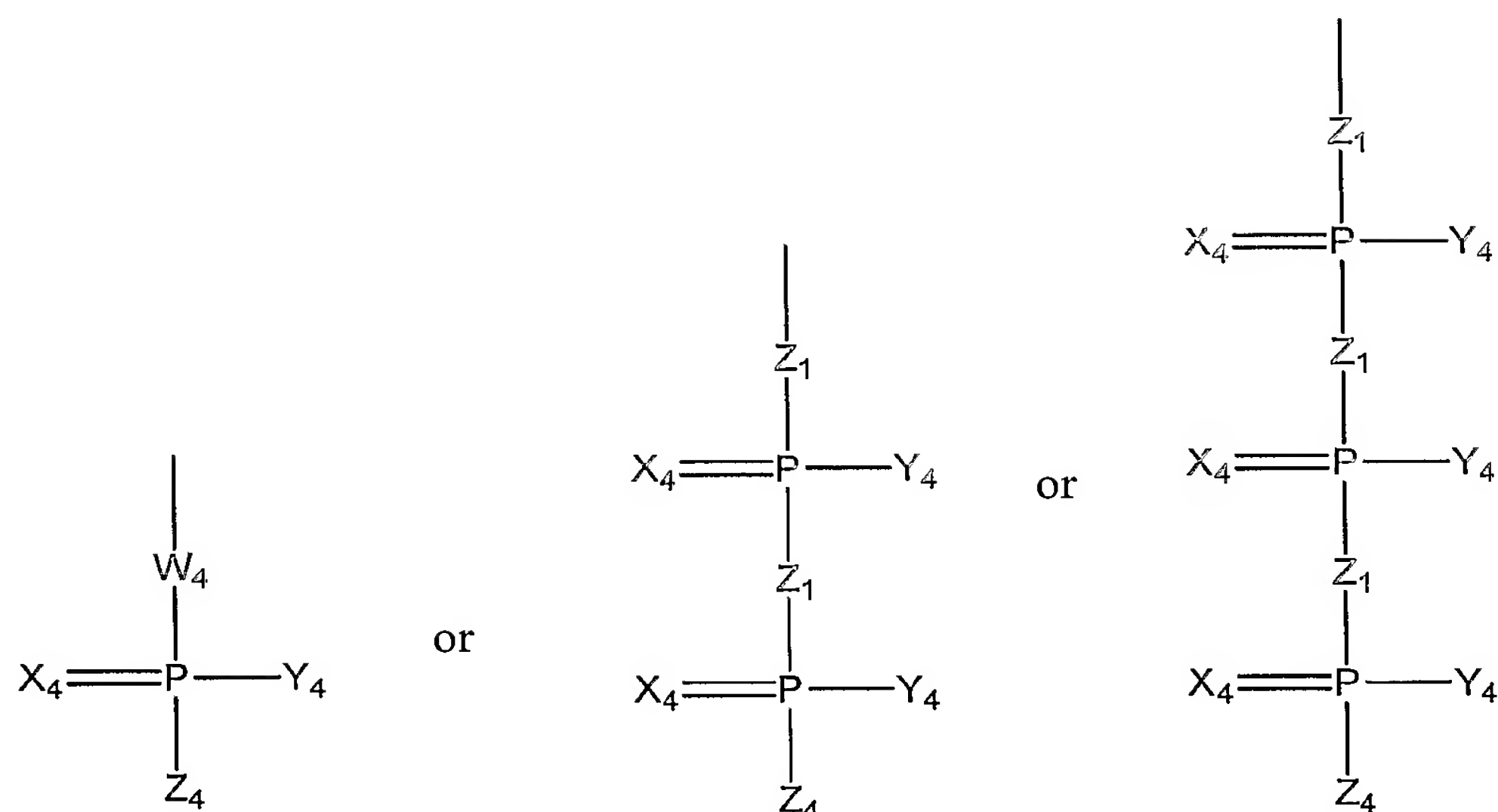
5

 $A^2$  is:

10

 $A^3$  is:

A<sup>4</sup> is:



5

; H; Z<sup>4</sup>; an inverted nucleotide; an abasic nucleotide; or absent.

W<sup>1</sup> is OH, (CH<sub>2</sub>)<sub>n</sub>R<sup>10</sup>, (CH<sub>2</sub>)<sub>n</sub>NHR<sup>10</sup>, (CH<sub>2</sub>)<sub>n</sub>OR<sup>10</sup>, (CH<sub>2</sub>)<sub>n</sub>SR<sup>10</sup>; O(CH<sub>2</sub>)<sub>n</sub>R<sup>10</sup>; O(CH<sub>2</sub>)<sub>n</sub>OR<sup>10</sup>, O(CH<sub>2</sub>)<sub>n</sub>NR<sup>10</sup>, O(CH<sub>2</sub>)<sub>n</sub>SR<sup>10</sup>; O(CH<sub>2</sub>)<sub>n</sub>SS(CH<sub>2</sub>)<sub>n</sub>OR<sup>10</sup>, O(CH<sub>2</sub>)<sub>n</sub>C(O)OR<sup>10</sup>, NH(CH<sub>2</sub>)<sub>n</sub>R<sup>10</sup>; NH(CH<sub>2</sub>)<sub>n</sub>NR<sup>10</sup>; NH(CH<sub>2</sub>)<sub>n</sub>OR<sup>10</sup>, NH(CH<sub>2</sub>)<sub>n</sub>SR<sup>10</sup>; S(CH<sub>2</sub>)<sub>n</sub>R<sup>10</sup>, S(CH<sub>2</sub>)<sub>n</sub>NR<sup>10</sup>, S(CH<sub>2</sub>)<sub>n</sub>OR<sup>10</sup>, S(CH<sub>2</sub>)<sub>n</sub>SR<sup>10</sup> O(CH<sub>2</sub>CH<sub>2</sub>O)<sub>m</sub>CH<sub>2</sub>CH<sub>2</sub>OR<sup>10</sup>; O(CH<sub>2</sub>CH<sub>2</sub>O)<sub>m</sub>CH<sub>2</sub>CH<sub>2</sub>NHR<sup>10</sup>, NH(CH<sub>2</sub>CH<sub>2</sub>NH)<sub>m</sub>CH<sub>2</sub>CH<sub>2</sub>NHR<sup>10</sup>; Q-R<sup>10</sup>, O-Q-R<sup>10</sup> N-Q-R<sup>10</sup>, S-Q-R<sup>10</sup> or -O-. W<sup>4</sup> is O, CH<sub>2</sub>, NH, or S.

X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, and X<sup>4</sup> are each, independently, O or S.  
Y<sup>1</sup>, Y<sup>2</sup>, Y<sup>3</sup>, and Y<sup>4</sup> are each, independently, OH, O<sup>-</sup>, OR<sup>8</sup>, S, Se, BH<sub>3</sub><sup>-</sup>, H, NHR<sup>9</sup>, N(R<sup>9</sup>)<sub>2</sub> alkyl, cycloalkyl, aralkyl, aryl, or heteroaryl, each of which may be optionally substituted.

Z<sup>1</sup>, Z<sup>2</sup>, and Z<sup>3</sup> are each independently O, CH<sub>2</sub>, NH, or S. Z<sup>4</sup> is OH, (CH<sub>2</sub>)<sub>n</sub>R<sup>10</sup>, (CH<sub>2</sub>)<sub>n</sub>NHR<sup>10</sup>, (CH<sub>2</sub>)<sub>n</sub>OR<sup>10</sup>, (CH<sub>2</sub>)<sub>n</sub>SR<sup>10</sup>; O(CH<sub>2</sub>)<sub>n</sub>R<sup>10</sup>; O(CH<sub>2</sub>)<sub>n</sub>OR<sup>10</sup>, O(CH<sub>2</sub>)<sub>n</sub>NR<sup>10</sup>, O(CH<sub>2</sub>)<sub>n</sub>SR<sup>10</sup>, O(CH<sub>2</sub>)<sub>n</sub>SS(CH<sub>2</sub>)<sub>n</sub>OR<sup>10</sup>, O(CH<sub>2</sub>)<sub>n</sub>C(O)OR<sup>10</sup>; NH(CH<sub>2</sub>)<sub>n</sub>R<sup>10</sup>; NH(CH<sub>2</sub>)<sub>n</sub>NR<sup>10</sup>; NH(CH<sub>2</sub>)<sub>n</sub>OR<sup>10</sup>, NH(CH<sub>2</sub>)<sub>n</sub>SR<sup>10</sup>; S(CH<sub>2</sub>)<sub>n</sub>R<sup>10</sup>, S(CH<sub>2</sub>)<sub>n</sub>NR<sup>10</sup>, S(CH<sub>2</sub>)<sub>n</sub>OR<sup>10</sup>, S(CH<sub>2</sub>)<sub>n</sub>SR<sup>10</sup>



$O(CH_2CH_2O)_mCH_2CH_2OR^{10}$ ,  $O(CH_2CH_2O)_mCH_2CH_2NHR^{10}$ ,  
 $NH(CH_2CH_2NH)_mCH_2CH_2NHR^{10}$ ;  $Q-R^{10}$ ,  $O-Q-R^{10}$ ,  $N-Q-R^{10}$ ,  $S-Q-R^{10}$ .

x is 5-100, chosen to comply with a length for an RNA agent described herein.

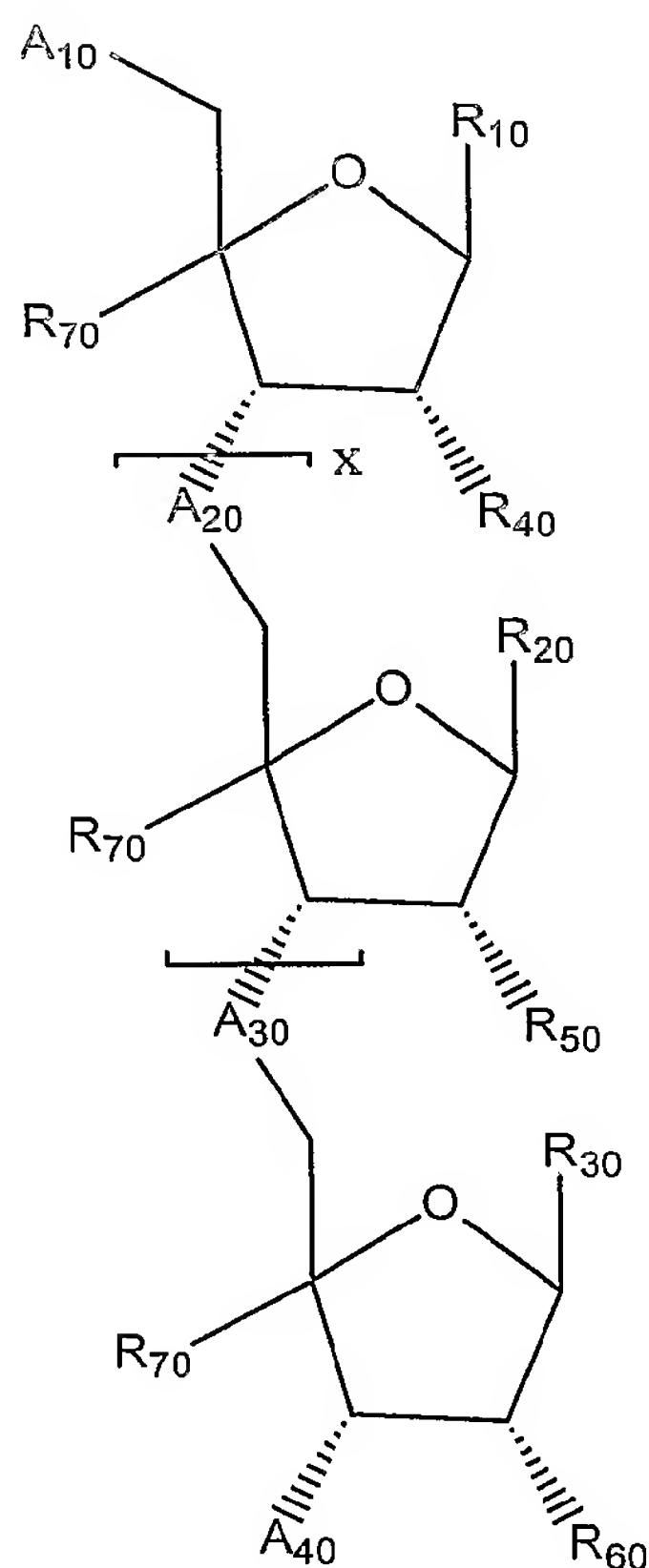
$R^7$  is H; or is together combined with  $R^4$ ,  $R^5$ , or  $R^6$  to form an  $[-O-CH_2-]$  covalently  
 5 bound bridge between the sugar 2' and 4' carbons.

$R^8$  is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, amino acid, or sugar;  $R^9$   
 is  $NH_2$ , alkylamino, dialkylamino, heterocyclyl, arylamino, diaryl amino, heteroaryl amino,  
 diheteroaryl amino, or amino acid; and  $R^{10}$  is H; fluorophore (pyrene, TAMRA, fluorescein,  
 Cy3 or Cy5 dyes); sulfur, silicon, boron or ester protecting group; intercalating agents (*e.g.*  
 10 acridines), cross-linkers (*e.g.* psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin,  
 Sapphyrin), polycyclic aromatic hydrocarbons (*e.g.*, phenazine, dihydrophenazine), artificial  
 endonucleases (*e.g.* EDTA), lipophilic carriers (cholesterol, cholic acid, adamantane acetic  
 acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol,  
 geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl  
 15 group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid,  
 dimethoxytrityl, or phenoxazine) and peptide conjugates (*e.g.*, antennapedia peptide, Tat  
 peptide), alkylating agents, phosphate, amino, mercapto, PEG (*e.g.*, PEG-40K), MPEG,  
 [MPEG]<sub>2</sub>, polyamino; alkyl, cycloalkyl, aryl, aralkyl, heteroaryl; radiolabelled markers,  
 enzymes, haptens (*e.g.* biotin), transport/absorption facilitators (*e.g.*, aspirin, vitamin E, folic  
 20 acid), synthetic ribonucleases (*e.g.*, imidazole, bisimidazole, histamine, imidazole clusters,  
 acridine-imidazole conjugates, Eu<sup>3+</sup> complexes of tetraazamacrocycles); or an RNA agent.  
 m is 0-1,000,000, and n is 0-20. Q is a spacer selected from the group consisting of abasic  
 sugar, amide, carboxy, oxyamine, oxyimine, thioether, disulfide, thiourea, sulfonamide, or  
 morpholino, biotin or fluorescein reagents.

25

30

Preferred RNA agents in which the entire phosphate group has been replaced have the following structure (see Formula 3 below):



FORMULA 3

Referring to Formula 3, A<sup>10</sup>-A<sup>40</sup> is L-G-L; A<sup>10</sup> and/or A<sup>40</sup> may be absent, in which L is a linker, wherein one or both L may be present or absent and is selected from the group consisting of CH<sub>2</sub>(CH<sub>2</sub>)<sub>g</sub>; N(CH<sub>2</sub>)<sub>g</sub>; O(CH<sub>2</sub>)<sub>g</sub>; S(CH<sub>2</sub>)<sub>g</sub>. G is a functional group selected from the group consisting of siloxane, carbonate, carboxymethyl, carbamate, amide, thioether, ethylene oxide linker, sulfonate, sulfonamide, thioformacetal, formacetal, oxime, methyleneimino, methylenemethylimino, methylenehydrazo, methylenedimethylhydrazo and methyleneoxymethylimino.

$R^{10}$ ,  $R^{20}$ , and  $R^{30}$  are each, independently, H, (*i.e.* abasic nucleotides), adenine, guanine, cytosine and uracil, inosine, thymine, xanthine, hypoxanthine, nubularine, tubercidine, isoguanisine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 5-halouracil and  
 5 cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 5-halouracil, 5-(2-aminopropyl)uracil, 5-amino allyl uracil, 8-halo, amino, thiol, thioalkyl, hydroxyl and other 8-substituted adenines and guanines, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine, 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine, dihydrouracil, 3-deaza-5-azacytosine, 2-aminopurine, 5-alkyluracil, 7-alkylguanine, 5-alkyl cytosine, 7-deazaadenine, 7-deazaguanine, N6, N6-dimethyladenine, 2,6-diaminopurine, 5-amino-allyl-uracil, N3-methyluracil substituted 1,2,4-triazoles, 2-pyridinone, 5-nitroindole, 3-nitropyrrole, 5-methoxyuracil, uracil-5-oxyacetic acid, 5-methoxycarbonylmethyluracil, 5-methyl-2-  
 15 thiouracil, 5-methoxycarbonylmethyl-2-thiouracil, 5-methylaminomethyl-2-thiouracil, 3-(3-amino-3carboxypropyl)uracil, 3-methylcytosine, 5-methylcytosine, N<sup>4</sup>-acetyl cytosine, 2-thiocytosine, N6-methyladenine, N6-isopentyladenine, 2-methylthio-N6-isopentenyladenine, N-methylguanines, or O-alkylated bases.

$R^{40}$ ,  $R^{50}$ , and  $R^{60}$  are each, independently,  $OR^8$ ,  $O(CH_2CH_2O)_mCH_2CH_2OR^8$ ;  
 20  $O(CH_2)_nR^9$ ;  $O(CH_2)_nOR^9$ , H; halo;  $NH_2$ ;  $NHR^8$ ;  $N(R^8)_2$ ;  $NH(CH_2CH_2NH)_mCH_2CH_2R^9$ ;  $NHC(O)R^8$ ; cyano; mercapto,  $SR^7$ ; alkyl-thio-alkyl; alkyl, aralkyl, cycloalkyl, aryl, heteroaryl, alkenyl, alkynyl, each of which may be optionally substituted with halo, hydroxy, oxo, nitro, haloalkyl, alkyl, alkaryl, aryl, aralkyl, alkoxy, aryloxy, amino, alkylamino, dialkylamino, heterocyclyl, arylamino, diaryl amino, heteroaryl amino, diheteroaryl amino,  
 25 acylamino, alkylcarbamoyl, arylcarbamoyl, aminoalkyl, alkoxycarbonyl, carboxy, hydroxyalkyl, alkanesulfonyl, alkanesulfonamido, arenesulfonamido, aralkylsulfonamido, alkylcarbonyl, acyloxy, cyano, and ureido groups; or  $R^{40}$ ,  $R^{50}$ , or  $R^{60}$  together combine with  $R^{70}$  to form an  $[-O-CH_2-]$  covalently bound bridge between the sugar 2' and 4' carbons.

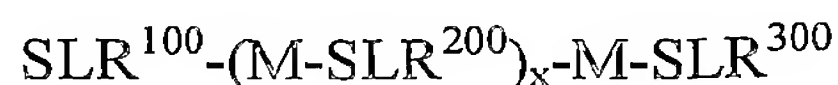
x is 5-100 or chosen to comply with a length for an RNA agent described herein.

30  $R^{70}$  is H; or is together combined with  $R^{40}$ ,  $R^{50}$ , or  $R^{60}$  to form an  $[-O-CH_2-]$  covalently bound bridge between the sugar 2' and 4' carbons.

$R^8$  is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, amino acid, or sugar; and  $R^9$  is  $NH_2$ , alkylamino, dialkylamino, heterocyclyl, arylamino, diaryl amino, heteroaryl amino, diheteroaryl amino, or amino acid.  $m$  is 0-1,000,000,  $n$  is 0-20, and  $g$  is 0-2.

Preferred nucleoside surrogates have the following structure (see Formula 4 below):

5



#### FORMULA 4

S is a nucleoside surrogate selected from the group consisting of mophilino,  
 10 cyclobutyl, pyrrolidine and peptide nucleic acid. L is a linker and is selected from the group consisting of  $CH_2(CH_2)_g$ ;  $N(CH_2)_g$ ;  $O(CH_2)_g$ ;  $S(CH_2)_g$ ;  $-C(O)(CH_2)_n$ -or may be absent. M is an amide bond; sulfonamide; sulfinate; phosphate group; modified phosphate group as described herein; or may be absent.

$R^{100}$ ,  $R^{200}$ , and  $R^{300}$  are each, independently, H (*i.e.*, abasic nucleotides), adenine,  
 15 guanine, cytosine and uracil, inosine, thymine, xanthine, hypoxanthine, nubularine, tubercidine, isoguanisine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 5-halouracil, 5-(2-aminopropyl)uracil, 5-amino allyl uracil, 8-  
 20 halo, amino, thiol, thioalkyl, hydroxyl and other 8-substituted adenines and guanines, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine, 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine, dihydrouracil, 3-deaza-5-azacytosine, 2-aminopurine, 5-alkyluracil, 7-alkylguanine, 5-alkyl cytosine, 7-deazaadenine,  
 25 7-deazaguanine, N6, N6-dimethyladenine, 2,6-diaminopurine, 5-amino-allyl-uracil, N3-methyluracil substituted 1, 2, 4,-triazoles, 2-pyridinones, 5-nitroindole, 3-nitropyrrole, 5-methoxyuracil, uracil-5-oxyacetic acid, 5-methoxycarbonylmethyluracil, 5-methyl-2-thiouracil, 5-methoxycarbonylmethyl-2-thiouracil, 5-methylaminomethyl-2-thiouracil, 3-(3-amino-3carboxypropyl)uracil, 3-methylcytosine, 5-methylcytosine,  $N^4$ -acetyl cytosine, 2-  
 30 thiocytosine, N6-methyladenine, N6-isopentyladenine, 2-methylthio-N6-isopentenyladenine, N-methylguanines, or O-alkylated bases.

x is 5-100, or chosen to comply with a length for an RNA agent described herein; and g is 0-2.

#### Nuclease resistant monomers

5 In one aspect, the invention features a nuclease resistant monomer, or a an iRNA agent which incorporates a nuclease resistant monomer (NMR), such as those described herein and those described in copending, co-owned United States Provisional Application Serial No. 60/469,612 (Attorney Docket No. 14174-069P01), filed on May 9, 2003, which is hereby incorporated by reference.

10 In addition, the invention includes iRNA agents having a NMR and another element described herein. E.g., the invention includes an iRNA agent described herein, e.g., a palindromic iRNA agent, an iRNA agent having a non canonical pairing, an iRNA agent which targets a gene described herein, e.g., a gene active in the liver, an iRNA agent having an architecture or structure described herein, an iRNA associated with an amphipathic  
15 delivery agent described herein, an iRNA associated with a drug delivery module described herein, an iRNA agent administered as described herein, or an iRNA agent formulated as described herein, which also incorporates a NMR.

An iRNA agent can include monomers which have been modified so as to inhibit degradation, e.g., by nucleases, e.g., endonucleases or exonucleases, found in the body of a  
20 subject. These monomers are referred to herein as NRM's, or nuclease resistance promoting monomers or modifications. In many cases these modifications will modulate other properties of the iRNA agent as well, e.g., the ability to interact with a protein, e.g., a transport protein, e.g., serum albumin, or a member of the RISC (RNA-induced Silencing Complex), or the ability of the first and second sequences to form a duplex with one another  
25 or to form a duplex with another sequence, e.g., a target molecule.

While not wishing to be bound by theory, it is believed that modifications of the sugar, base, and/or phosphate backbone in an iRNA agent can enhance endonuclease and exonuclease resistance, and can enhance interactions with transporter proteins and one or more of the functional components of the RISC complex. Preferred modifications are those  
30 that increase exonuclease and endonuclease resistance and thus prolong the halflife of the iRNA agent prior to interaction with the RISC complex, but at the same time do not render



the iRNA agent resistant to endonuclease activity in the RISC complex. Again, while not wishing to be bound by any theory, it is believed that placement of the modifications at or near the 3' and/or 5' end of antisense strands can result in iRNA agents that meet the preferred nuclease resistance criteria delineated above. Again, still while not wishing to be bound by any theory, it is believed that placement of the modifications at e.g., the middle of a sense strand can result in iRNA agents that are relatively less likely to undergo off-targeting.

Modifications described herein can be incorporated into any double-stranded RNA and RNA-like molecule described herein, e.g., an iRNA agent. An iRNA agent may include a duplex comprising a hybridized sense and antisense strand, in which the antisense strand and/or the sense strand may include one or more of the modifications described herein. The anti sense strand may include modifications at the 3' end and/or the 5' end and/or at one or more positions that occur 1-6 (e.g., 1-5, 1-4, 1-3, 1-2) nucleotides from either end of the strand. The sense strand may include modifications at the 3' end and/or the 5' end and/or at any one of the intervening positions between the two ends of the strand. The iRNA agent may also include a duplex comprising two hybridized antisense strands. The first and/or the second antisense strand may include one or more of the modifications described herein. Thus, one and/or both antisense strands may include modifications at the 3' end and/or the 5' end and/or at one or more positions that occur 1-6 (e.g., 1-5, 1-4, 1-3, 1-2) nucleotides from either end of the strand. Particular configurations are discussed below.

Modifications that can be useful for producing iRNA agents that meet the preferred nuclease resistance criteria delineated above can include one or more of the following chemical and/or stereochemical modifications of the sugar, base, and/or phosphate backbone:

(i) chiral ( $S_P$ ) thioates. Thus, preferred NRM's include nucleotide dimers with an enriched or pure for a particular chiral form of a modified phosphate group containing a heteroatom at the nonbridging position, e.g.,  $S_P$  or  $R_P$ , at the position X, where this is the position normally occupied by the oxygen. The atom at X can also be S, Se,  $Nr_2$ , or  $Br_3$ . When X is S, enriched or chirally pure  $S_P$  linkage is preferred. Enriched means at least 70, 80, 90, 95, or 99% of the preferred form. Such NRM's are discussed in more detail below;

(ii) attachment of one or more cationic groups to the sugar, base, and/or the phosphorus atom of a phosphate or modified phosphate backbone moiety. Thus, preferred NRM's include monomers at the terminal position derivitized at a cationic group. As the 5'

end of an antisense sequence should have a terminal –OH or phosphate group this NRM is preferraly not used at th 5' end of an anti-sense sequence. The group should be attached at a position on the base which minimizes intererence with H bond formation and hybridization, e.g., away form the face which intereacts with the complementary base on the other strand, e.g., at the 5' position of a pyrimidine or a 7-position of a purine. These are discussed in more detail below;

(iii) nonphosphate linkages at the termini. Thus, preferred NRM's include Non-phosphate linkages, e.g., a linkage of 4 atoms which confers greater resistance to cleavage than does a phosphate bond. Examples include 3' CH<sub>2</sub>-NCH<sub>3</sub>-O-CH<sub>2</sub>-5' and 3' CH<sub>2</sub>-NH-(O=)-CH<sub>2</sub>-5';

(iv) 3'-bridging thiophosphates and 5'-bridging thiophosphates. Thus, preferred NRM's can inlcuded these structures;

(v) L-RNA, 2'-5' likages, inverted linkages, a-nucleosides. Thus, other preferred NRM's include: L nucleosides and dimeric nucleotides derived from L-nucleosides; 2'-5' phosphate, non-phosphate and modified phosphate linkages (e.g., thiophospahtes, phosphoramidates and boronophosphates); dimers having inverted linkages, e.g., 3'-3' or 5'-5' linkages; monomers having an alpha linkage at the 1' site on the sugar, e.g., the structures described herein having an alpha linkage;

(vi) conjugate groups. Thus, preferred NRM's can include e.g., a targeting moiety or a conjugated ligand described herein conjugated with the monomer, e.g., through the sugar , base, or backbone ;

(vi) abasic linkages. Thus, preferred NRM's can include an abasic monomer, e.g., an abasic monomer as described herein (e.g., a nucleobaseless monomer); an aromatic or heterocyclic or polyheterocyclic aromatic monomer as described herein.; and

(vii) 5'-phosphonates and 5'-phosphate prodrugs. Thus, preferred NRM's include monomers, preferably at the terminal position, e.g., the 5' position, in which one or more atoms of the phosphate group is derivatized with a protecting group, which protecting group or groups, are removed as a result of the action of a component in the subject's body, e.g, a carboxyesterase or an enzyme present in the subject's body. E.g., a phosphate prodrug in which a carboxy esterase cleaves the protected molecule resulting in the production of a

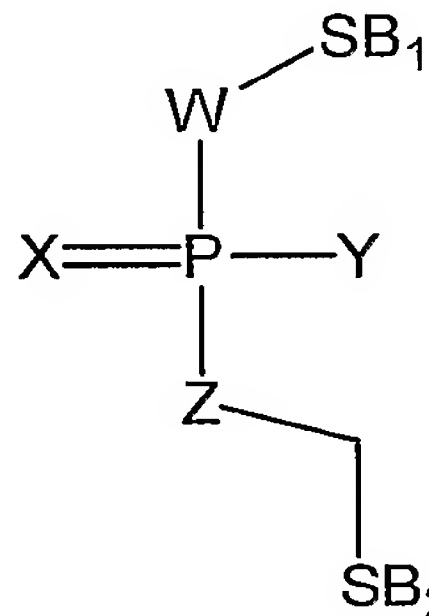
thioate anion which attacks a carbon adjacent to the O of a phosphate and resulting in the production of an unprotected phosphate.

One or more different NRM modifications can be introduced into an iRNA agent or into a sequence of an iRNA agent. An NRM modification can be used more than once in a sequence or in an iRNA agent. As some NRM's interfere with hybridization the total number incorporated, should be such that acceptable levels of iRNA agent duplex formation are maintained.

In some embodiments NRM modifications are introduced into the terminal the cleavage site or in the cleavage region of a sequence (a sense strand or sequence) which does not target a desired sequence or gene in the subject. This can reduce off-target silencing.

#### *Chiral S<sub>P</sub> Thioates*

A modification can include the alteration, *e.g.*, replacement, of one or both of the non-linking (X and Y) phosphate oxygens and/or of one or more of the linking (W and Z) phosphate oxygens. Formula X below depicts a phosphate moiety linking two sugar/sugar surrogate-base moities, SB<sub>1</sub> and SB<sub>2</sub>.



FORMULA X

20

In certain embodiments, one of the non-linking phosphate oxygens in the phosphate backbone moiety (X and Y) can be replaced by any one of the following: S, Se, BR<sub>3</sub> (R is hydrogen, alkyl, aryl, etc.), C (i.e., an alkyl group, an aryl group, etc.), H, NR<sub>2</sub> (R is hydrogen, alkyl, aryl, etc.), or OR (R is alkyl or aryl). The phosphorus atom in an unmodified phosphate group is achiral. However, replacement of one of the non-linking

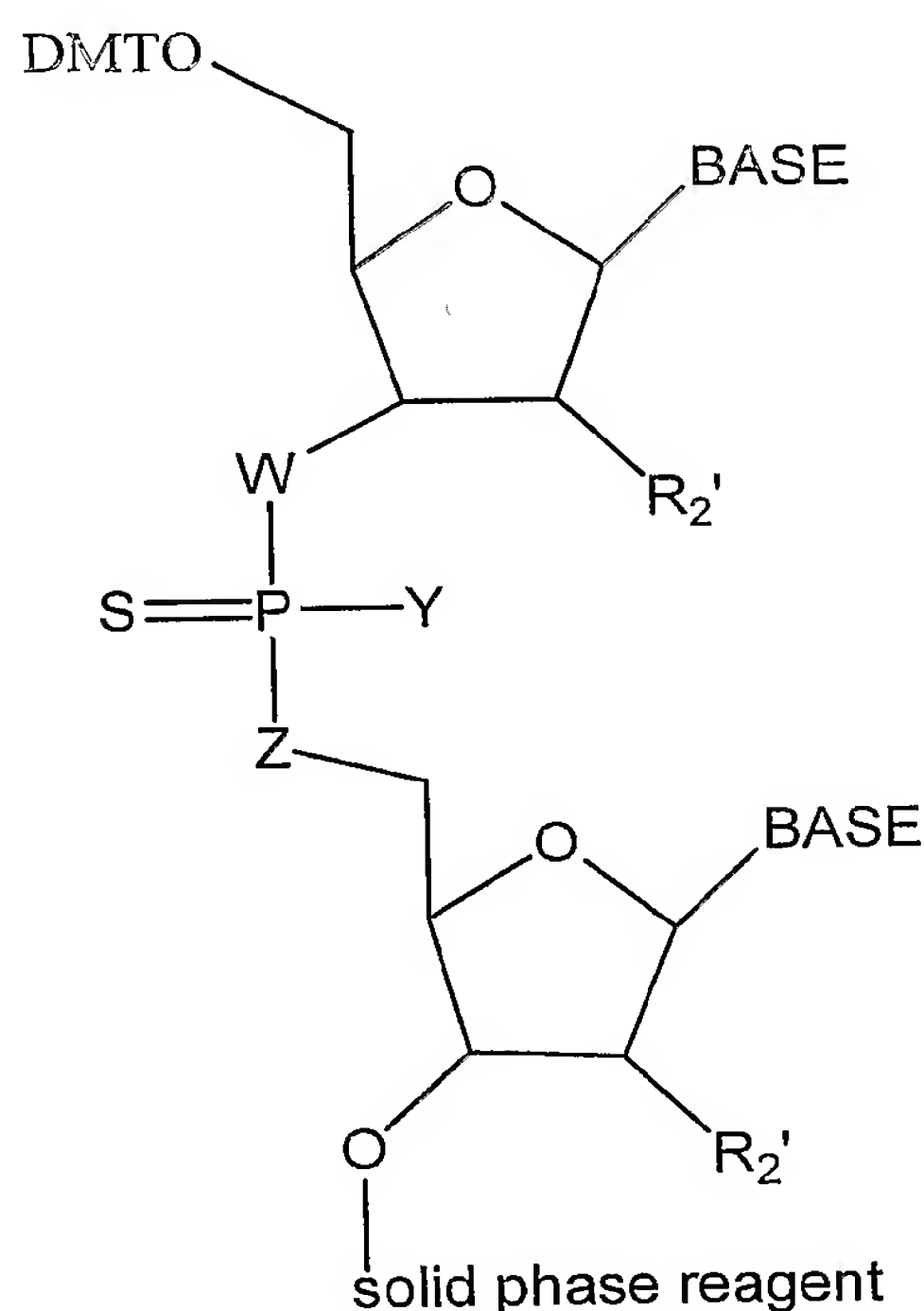
25

oxygen with one of the above atoms or groups of atoms renders the phosphorus atom chiral; in other words a phosphorus atom in a phosphate group modified in this way is a stereogenic center. The stereogenic phosphorus atom can possess either the “R” configuration (herein  $R_P$ ) or the “S” configuration (herein  $S_P$ ). Thus if 60% of a population of stereogenic  
5 phosphorus atoms have the  $R_P$  configuration, then the remaining 40% of the population of stereogenic phosphorus atoms have the  $S_P$  configuration.

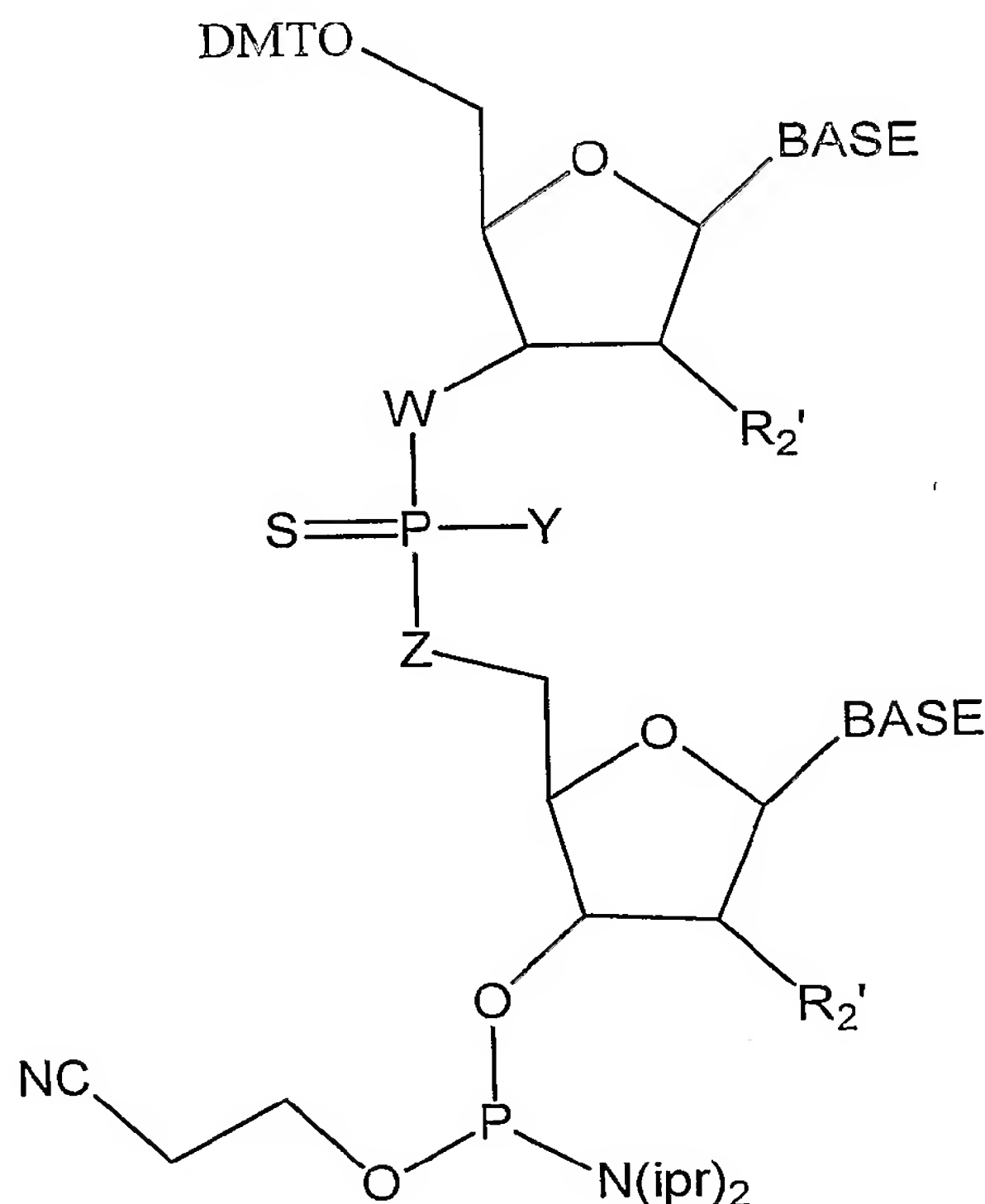
In some embodiments, iRNA agents, having phosphate groups in which a phosphate non-linking oxygen has been replaced by another atom or group of atoms, may contain a population of stereogenic phosphorus atoms in which at least about 50% of these atoms (e.g.,  
10 at least about 60% of these atoms, at least about 70% of these atoms, at least about 80% of these atoms, at least about 90% of these atoms, at least about 95% of these atoms, at least about 98% of these atoms, at least about 99% of these atoms) have the  $S_P$  configuration. Alternatively, iRNA agents having phosphate groups in which a phosphate non-linking oxygen has been replaced by another atom or group of atoms may contain a population of  
15 stereogenic phosphorus atoms in which at least about 50% of these atoms (e.g., at least about 60% of these atoms, at least about 70% of these atoms, at least about 80% of these atoms, at least about 90% of these atoms, at least about 95% of these atoms, at least about 98% of these atoms, at least about 99% of these atoms) have the  $R_P$  configuration. In other embodiments, the population of stereogenic phosphorus atoms may have the  $S_P$   
20 configuration and may be substantially free of stereogenic phosphorus atoms having the  $R_P$  configuration. In still other embodiments, the population of stereogenic phosphorus atoms may have the  $R_P$  configuration and may be substantially free of stereogenic phosphorus atoms having the  $S_P$  configuration. As used herein, the phrase “substantially free of stereogenic phosphorus atoms having the  $R_P$  configuration” means that moieties containing  
25 stereogenic phosphorus atoms having the  $R_P$  configuration cannot be detected by conventional methods known in the art (chiral HPLC,  $^1H$  NMR analysis using chiral shift reagents, etc.). As used herein, the phrase “substantially free of stereogenic phosphorus atoms having the  $S_P$  configuration” means that moieties containing stereogenic phosphorus atoms having the  $S_P$  configuration cannot be detected by conventional methods known in the  
30 art (chiral HPLC,  $^1H$  NMR analysis using chiral shift reagents, etc.).

In a preferred embodiment, modified iRNA agents contain a phosphorothioate group, i.e., a phosphate groups in which a phosphate non-linking oxygen has been replaced by a sulfur atom. In an especially preferred embodiment, the population of phosphorothioate stereogenic phosphorus atoms may have the  $S_P$  configuration and be substantially free of stereogenic phosphorus atoms having the  $R_P$  configuration.

Phosphorothioates may be incorporated into iRNA agents using dimers e.g., formulas X-1 and X-2. The former can be used to introduce phosphorothioate



X-1



X-2

at the 3' end of a strand, while the latter can be used to introduce this modification at the 5' end or at a position that occurs e.g., 1, 2, 3, 4, 5, or 6 nucleotides from either end of the strand. In the above formulas, Y can be 2-cyanoethoxy, W and Z can be O,  $R_2'$  can be, e.g., a substituent that can impart the C-3' endo configuration to the sugar (e.g., OH, F,  $OCH_3$ ), DMT is dimethoxytrityl, and "BASE" can be a natural, unusual, or a universal base.



X-1 and X-2 can be prepared using chiral reagents or directing groups that can result in phosphorothioate-containing dimers having a population of stereogenic phosphorus atoms having essentially only the  $R_P$  configuration (i.e., being substantially free of the  $S_P$  configuration) or only the  $S_P$  configuration (i.e., being substantially free of the  $R_P$  configuration). Alternatively, dimers can be prepared having a population of stereogenic phosphorus atoms in which about 50% of the atoms have the  $R_P$  configuration and about 50% of the atoms have the  $S_P$  configuration. Dimers having stereogenic phosphorus atoms with the  $R_P$  configuration can be identified and separated from dimers having stereogenic phosphorus atoms with the  $S_P$  configuration using e.g., enzymatic degradation and/or conventional chromatography techniques.

### *Cationic Groups*

Modifications can also include attachment of one or more cationic groups to the sugar, base, and/or the phosphorus atom of a phosphate or modified phosphate backbone moiety. A cationic group can be attached to any atom capable of substitution on a natural, unusual or universal base. A preferred position is one that does not interfere with hybridization, i.e., does not interfere with the hydrogen bonding interactions needed for base pairing. A cationic group can be attached e.g., through the C2' position of a sugar or analogous position in a cyclic or acyclic sugar surrogate. Cationic groups can include e.g., protonated amino groups, derived from e.g., O-AMINE (AMINE =  $NH_2$ ; alkylamino, dialkylamino, heterocyclyl, arylamino, diaryl amino, heteroaryl amino, or diheteroaryl amino, ethylene diamine, polyamino); aminoalkoxy, e.g.,  $O(CH_2)_n$ AMINE, (e.g., AMINE =  $NH_2$ ; alkylamino, dialkylamino, heterocyclyl, arylamino, diaryl amino, heteroaryl amino, or diheteroaryl amino, ethylene diamine, polyamino); amino (e.g.  $NH_2$ ; alkylamino, dialkylamino, heterocyclyl, arylamino, diaryl amino, heteroaryl amino, diheteroaryl amino, or amino acid); or  $NH(CH_2CH_2NH)_nCH_2CH_2$ -AMINE (AMINE =  $NH_2$ ; alkylamino, dialkylamino, heterocyclyl, arylamino, diaryl amino, heteroaryl amino, or diheteroaryl amino).

### *Nonphosphate Linkages*

Modifications can also include the incorporation of nonphosphate linkages at the 5' and/or 3' end of a strand. Examples of nonphosphate linkages which can replace the

phosphate group include methyl phosphonate, hydroxylamino, siloxane, carbonate, carboxymethyl, carbamate, amide, thioether, ethylene oxide linker, sulfonate, sulfonamide, thioformacetal, formacetal, oxime, methyleneimino, methylenemethylimino, methylenehydrazo, methylenedimethylhydrazo and methyleneoxymethylimino. Preferred  
 5 replacements include the methyl phosphonate and hydroxylamino groups.

*3'-bridging thiophosphates and 5'-bridging thiophosphates; locked-RNA, 2'-5' linkages, inverted linkages,  $\alpha$ -nucleosides; conjugate groups; abasic linkages; and 5'-phosphonates and 5'-phosphate prodrugs*

10 Referring to formula X above, modifications can include replacement of one of the bridging or linking phosphate oxygens in the phosphate backbone moiety (W and Z). Unlike the situation where only one of X or Y is altered, the phosphorus center in the phosphorodithioates is achiral which precludes the formation of iRNA agents containing a stereogenic phosphorus atom..

15 Modifications can also include linking two sugars via a phosphate or modified phosphate group through the 2' position of a first sugar and the 5' position of a second sugar. Also contemplated are inverted linkages in which both a first and second sugar are each linked through the respective 3' positions. Modified RNA's can also include "abasic" sugars, which lack a nucleobase at C-1'. The sugar group can also contain one or more carbons that  
 20 possess the opposite stereochemical configuration than that of the corresponding carbon in ribose. Thus, a modified iRNA agent can include nucleotides containing *e.g.*, arabinose, as the sugar. In another subset of this modification, the natural, unusual, or universal base may have the  $\alpha$ -configuration. Modifications can also include L-RNA.

25 Modifications can also include 5'-phosphonates, *e.g.*,  $P(O)(O^-)_2-X-C^{5'}\text{-sugar}$  ( $X=CH_2, CF_2, CHF$  and 5'-phosphate prodrugs, *e.g.*,  $P(O)[OCH_2CH_2SC(O)R]_2CH_2C^{5'}\text{-sugar}$ . In the latter case, the prodrug groups may be decomposed *via* reaction first with carboxy esterases. The remaining ethyl thiolate group via intramolecular  $S_N2$  displacement can depart as episulfide to afford the underivatized phosphate group.

30 Modification can also include the addition of conjugating groups described elsewhere herein, which are preferably attached to an iRNA agent through any amino group available for conjugation.

Nuclease resistant modifications include some which can be placed only at the terminus and others which can go at any position. Generally the modifications that can inhibit hybridization so it is preferably to use them only in terminal regions, and preferable to not use them at the cleavage site or in the cleavage region of an sequence which targets a subject sequence or gene.. The can be used anywhere in a sense sequence, provided that sufficient hybridization between the two sequences of the iRNA agent is maintained. In some embodiments it is desirable to put the NRM at the cleavage site or in the cleavage region of a sequence which does not target a subject sequence or gene, as it can minimize off-target silencing.

In addition, an iRNA agent described herein can have an overhang which does not form a duplex structure with the other sequence of the iRNA agent—it is an overhang, but it does hybridize, either with itself, or with another nucleic acid, other than the other sequence of the iRNA agent.

In most cases, the nuclease-resistance promoting modifications will be distributed differently depending on whether the sequence will target a sequence in the subject (often referred to as an anti-sense sequence) or will not target a sequence in the subject (often referred to as a sense sequence). If a sequence is to target a sequence in the subject, modifications which interfere with or inhibit endonuclease cleavage should not be inserted in the region which is subject to RISC mediated cleavage, e.g., the cleavage site or the cleavage region (As described in Elbashir *et al.*, 2001, Genes and Dev. 15: 188, hereby incorporated by reference, cleavage of the target occurs about in the middle of a 20 or 21 nt guide RNA, or about 10 or 11 nucleotides upstream of the first nucleotide which is complementary to the guide sequence. As used herein cleavage site refers to the nucleotide on either side of the cleavage site, on the target or on the iRNA agent strand which hybridizes to it. Cleavage region means an nucleotide with 1, 2, or 3 nucleotides of the cleavage site, in either direction.)

Such modifications can be introduced into the terminal regions, e.g., at the terminal position or with 2, 3, 4, or 5 positions of the terminus, of a sequence which targets or a sequence which does not target a sequence in the subject.

An iRNA agent can have a first and a second strand chosen from the following:

a first strand which does not target a sequence and which has an NRM modification at or within 1, 2, 3, 4, 5, or 6 positions from the 3' end;

a first strand which does not target a sequence and which has an NRM modification at or within 1, 2, 3, 4, 5, or 6 positions from the 5' end;

a first strand which does not target a sequence and which has an NRM modification at or within 1, 2, 3, 4, 5, or 6 positions from the 3' end and which has a NRM modification at  
5 or within 1, 2, 3, 4, 5, or 6 positions from the 5' end;

a first strand which does not target a sequence and which has an NRM modification at the cleavage site or in the cleavage region;

a first strand which does not target a sequence and which has an NRM modification at the cleavage site or in the cleavage region and one or more of an NRM modification at or  
10 within 1, 2, 3, 4, 5, or 6 positions from the 3' end, a NRM modification at or within 1, 2, 3, 4, 5, or 6 positions from the 5' end, or NRM modifications at or within 1, 2, 3, 4, 5, or 6 positions from both the 3' and the 5' end; and

a second strand which targets a sequence and which has an NRM modification at or within 1, 2, 3, 4, 5, or 6 positions from the 3' end;

15 a second strand which targets a sequence and which has an NRM modification at or within 1, 2, 3, 4, 5, or 6 positions from the 5' end (5' end NRM modifications are preferentially not at the terminus but rather at a position 1, 2, 3, 4, 5, or 6 away from the 5' terminus of an antisense strand);

a second strand which targets a sequence and which has an NRM modification at or  
20 within 1, 2, 3, 4, 5, or 6 positions from the 3' end and which has a NRM modification at or within 1, 2, 3, 4, 5, or 6 positions from the 5' end;

a second strand which targets a sequence and which preferably does not have an NRM modification at the cleavage site or in the cleavage region;

a second strand which targets a sequence and which does not have an NRM  
25 modification at the cleavage site or in the cleavage region and one or more of an NRM modification at or within 1, 2, 3, 4, 5, or 6 positions from the 3' end, a NRM modification at or within 1, 2, 3, 4, 5, or 6 positions from the 5' end, or NRM modifications at or within 1, 2, 3, 4, 5, or 6 positions from both the 3' and the 5' end (5' end NRM modifications are preferentially not at the terminus but rather at a position 1, 2, 3, 4, 5, or 6 away from the 5'  
30 terminus of an antisense strand).

An iRNA agent can also target two sequences and can have a first and second strand chosen from:

a first strand which targets a sequence and which has an NRM modification at or within 1, 2, 3, 4, 5, or 6 positions from the 3' end;

5 a first strand which targets a sequence and which has an NRM modification at or within 1, 2, 3, 4, 5, or 6 positions from the 5' end (5' end NRM modifications are preferentially not at the terminus but rather at a position 1, 2, 3, 4, 5, or 6 away from the 5' terminus of an antisense strand);

10 a first strand which targets a sequence and which has an NRM modification at or within 1, 2, 3, 4, 5, or 6 positions from the 3' end and which has a NRM modification at or within 1, 2, 3, 4, 5, or 6 positions from the 5' end;

a first strand which targets a sequence and which preferably does not have an NRM modification at the cleavage site or in the cleavage region;

15 a first strand which targets a sequence and which does not have an NRM modification at the cleavage site or in the cleavage region and one or more of an NRM modification at or within 1, 2, 3, 4, 5, or 6 positions from the 3' end, a NRM modification at or within 1, 2, 3, 4, 5, or 6 positions from the 5' end, or NRM modifications at or within 1, 2, 3, 4, 5, or 6 positions from both the 3' and the 5' end (5' end NRM modifications are preferentially not at the terminus but rather at a position 1, 2, 3, 4, 5, or 6 away from the 5' terminus of an  
20 antisense strand) and

a second strand which targets a sequence and which has an NRM modification at or within 1, 2, 3, 4, 5, or 6 positions from the 3' end;

25 a second strand which targets a sequence and which has an NRM modification at or within 1, 2, 3, 4, 5, or 6 positions from the 5' end (5' end NRM modifications are preferentially not at the terminus but rather at a position 1, 2, 3, 4, 5, or 6 away from the 5' terminus of an antisense strand);

a second strand which targets a sequence and which has an NRM modification at or within 1, 2, 3, 4, 5, or 6 positions from the 3' end and which has a NRM modification at or within 1, 2, 3, 4, 5, or 6 positions from the 5' end;

30 a second strand which targets a sequence and which preferably does not have an NRM modification at the cleavage site or in the cleavage region;



a second strand which targets a sequence and which does not have an NRM modification at the cleavage site or in the cleavage region and one or more of an NRM modification at or within 1, 2, 3, 4, 5, or 6 positions from the 3' end, a NRM modification at or within 1, 2, 3, 4, 5, or 6 positions from the 5' end, or NRM modifications at or within 1, 2, 3, 4, 5, or 6 positions from both the 3' and the 5' end (5' end NRM modifications are preferentially not at the terminus but rather at a position 1, 2, 3, 4, 5, or 6 away from the 5' terminus of an antisense strand).

### **Ribose Mimics**

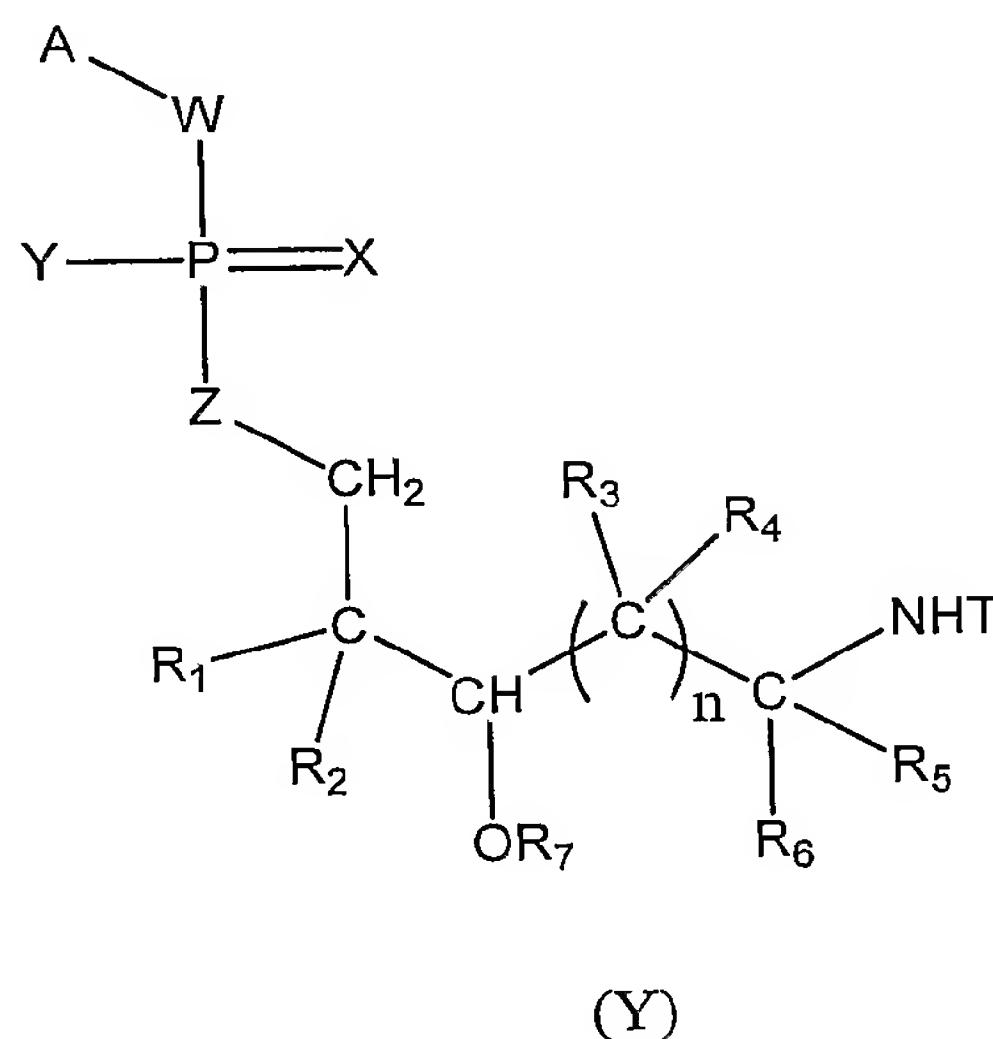
10 In one aspect, the invention features a ribose mimic, or an iRNA agent which incorporates a ribose mimic, such as those described herein and those described in copending co-owned United States Provisional Application Serial No. 60/454,962 (Attorney Docket No. 14174-064P01), filed on March 13, 2003, which is hereby incorporated by reference.

In addition, the invention includes iRNA agents having a ribose mimic and another  
15 element described herein. E.g., the invention includes an iRNA agent described herein, e.g., a palindromic iRNA agent, an iRNA agent having a non canonical pairing, an iRNA agent which targets a gene described herein, e.g., a gene active in the liver, an iRNA agent having an architecture or structure described herein, an iRNA associated with an amphipathic delivery agent described herein, an iRNA associated with a drug delivery module described  
20 herein, an iRNA agent administered as described herein, or an iRNA agent formulated as described herein, which also incorporates a ribose mimic.

Thus, an aspect of the invention features an iRNA agent that includes a secondary hydroxyl group, which can increase efficacy and/or confer nuclease resistance to the agent. Nucleases, e.g., cellular nucleases, can hydrolyze nucleic acid phosphodiester bonds,  
25 resulting in partial or complete degradation of the nucleic acid. The secondary hydroxy group confers nuclease resistance to an iRNA agent by rendering the iRNA agent less prone to nuclease degradation relative to an iRNA which lacks the modification. While not wishing to be bound by theory, it is believed that the presence of a secondary hydroxyl group on the iRNA agent can act as a structural mimic of a 3' ribose hydroxyl group, thereby  
30 causing it to be less susceptible to degradation.

The secondary hydroxyl group refers to an "OH" radical that is attached to a carbon atom substituted by two other carbons and a hydrogen. The secondary hydroxyl group that confers nuclease resistance as described above can be part of any acyclic carbon-containing group. The hydroxyl may also be part of any cyclic carbon-containing group, and preferably one or more of the following conditions is met (1) there is no ribose moiety between the hydroxyl group and the terminal phosphate group or (2) the hydroxyl group is not on a sugar moiety which is coupled to a base.. The hydroxyl group is located at least two bonds (e.g., at least three bonds away, at least four bonds away, at least five bonds away, at least six bonds away, at least seven bonds away, at least eight bonds away, at least nine bonds away, at least ten bonds away, etc.) from the terminal phosphate group phosphorus of the iRNA agent. In preferred embodiments, there are five intervening bonds between the terminal phosphate group phosphorus and the secondary hydroxyl group.

Preferred iRNA agent delivery modules with five intervening bonds between the terminal phosphate group phosphorus and the secondary hydroxyl group have the following structure (see formula Y below):



Referring to formula Y, A is an iRNA agent, including any iRNA agent described herein. The iRNA agent may be connected directly or indirectly (e.g., through a spacer or linker) to "W" of the phosphate group. These spacers or linkers can include e.g.,  $-(\text{CH}_2)_n-$ , -

$(\text{CH}_2)_n\text{N}-$ ,  $-(\text{CH}_2)_n\text{O}-$ ,  $-(\text{CH}_2)_n\text{S}-$ ,  $\text{O}(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2\text{OH}$  (e.g.,  $n = 3$  or  $6$ ), abasic sugars, amide, carboxy, amine, oxyamine, oxyimine, thioether, disulfide, thiourea, sulfonamide, or morpholino, or biotin and fluorescein reagents.

The iRNA agents can have a terminal phosphate group that is unmodified (e.g., W, X, Y, and Z are O) or modified. In a modified phosphate group, W and Z can be independently  
 5 NH, O, or S; and X and Y can be independently S, Se,  $\text{BH}_3^-$ ,  $\text{C}_1\text{-C}_6$  alkyl,  $\text{C}_6\text{-C}_{10}$  aryl, H, O,  $\text{O}^-$ , alkoxy or amino (including alkylamino, arylamino, etc.). Preferably, W, X and Z are O and Y is S.

$\text{R}_1$  and  $\text{R}_3$  are each, independently, hydrogen; or  $\text{C}_1\text{-C}_{100}$  alkyl, optionally substituted  
 10 with hydroxyl, amino, halo, phosphate or sulfate and/or may be optionally inserted with N, O, S, alkenyl or alkynyl.

$\text{R}_2$  is hydrogen;  $\text{C}_1\text{-C}_{100}$  alkyl, optionally substituted with hydroxyl, amino, halo, phosphate or sulfate and/or may be optionally inserted with N, O, S, alkenyl or alkynyl; or, when  $n$  is 1,  $\text{R}_2$  may be taken together with with  $\text{R}_4$  or  $\text{R}_6$  to form a ring of 5-12 atoms.

$\text{R}_4$  is hydrogen;  $\text{C}_1\text{-C}_{100}$  alkyl, optionally substituted with hydroxyl, amino, halo,  
 15 phosphate or sulfate and/or may be optionally inserted with N, O, S, alkenyl or alkynyl; or, when  $n$  is 1,  $\text{R}_4$  may be taken together with with  $\text{R}_2$  or  $\text{R}_5$  to form a ring of 5-12 atoms.

$\text{R}_5$  is hydrogen,  $\text{C}_1\text{-C}_{100}$  alkyl optionally substituted with hydroxyl, amino, halo, phosphate or sulfate and/or may be optionally inserted with N, O, S, alkenyl or alkynyl; or,  
 20 when  $n$  is 1,  $\text{R}_5$  may be taken together with with  $\text{R}_4$  to form a ring of 5-12 atoms.

$\text{R}_6$  is hydrogen,  $\text{C}_1\text{-C}_{100}$  alkyl, optionally substituted with hydroxyl, amino, halo, phosphate or sulfate and/or may be optionally inserted with N, O, S, alkenyl or alkynyl, or, when  $n$  is 1,  $\text{R}_6$  may be taken together with with  $\text{R}_2$  to form a ring of 6-10 atoms;

$\text{R}_7$  is hydrogen,  $\text{C}_1\text{-C}_{100}$  alkyl, or  $\text{C}(\text{O})(\text{CH}_2)_q\text{C}(\text{O})\text{NHR}_9$ ; T is hydrogen or a  
 25 functional group;  $n$  and  $q$  are each independently 1-100;  $\text{R}_8$  is  $\text{C}_1\text{-C}_{10}$  alkyl or  $\text{C}_6\text{-C}_{10}$  aryl; and  $\text{R}_9$  is hydrogen,  $\text{C}_1\text{-C}_{10}$  alkyl,  $\text{C}_6\text{-C}_{10}$  aryl or a solid support agent.

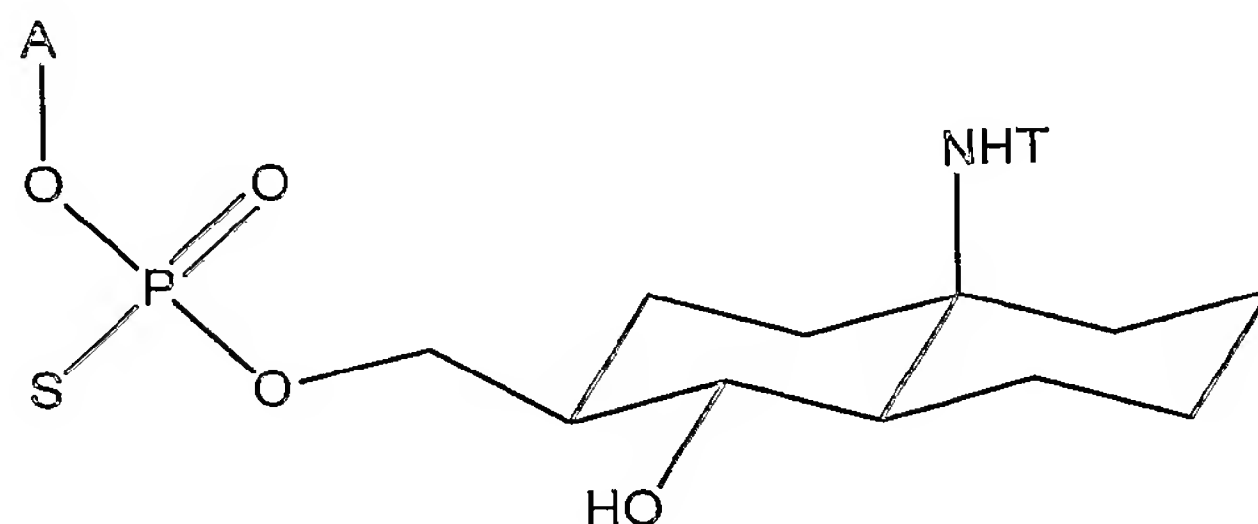
Preferred embodiments may include one of more of the following subsets of iRNA agent delivery modules.

In one subset of RNAi agent delivery modules, A can be connected directly or  
 30 indirectly through a terminal 3' or 5' ribose sugar carbon of the RNA agent.

In another subset of RNAi agent delivery modules, X, W, and Z are O and Y is S.

In still yet another subset of RNAi agent delivery modules, n is 1, and R<sub>2</sub> and R<sub>6</sub> are taken together to form a ring containing six atoms and R<sub>4</sub> and R<sub>5</sub> are taken together to form a ring containing six atoms. Preferably, the ring system is a *trans*-decalin. For example, the RNAi agent delivery module of this subset can include a compound of Formula (Y-1):

5



The functional group can be, for example, a targeting group (e.g., a steroid or a carbohydrate), a reporter group (e.g., a fluorophore), or a label (an isotopically labelled moiety). The targeting group can further include protein binding agents, endothelial cell  
 10 targeting groups (e.g., RGD peptides and mimetics), cancer cell targeting groups (e.g., folate Vitamin B12, Biotin), bone cell targeting groups (e.g., bisphosphonates, polyglutamates, polyaspartates), multivalent mannose (for e.g., macrophage testing), lactose, galactose, N-acetyl-galactosamine, monoclonal antibodies, glycoproteins, lectins, melanotropin, or thyrotropin.

15 As can be appreciated by the skilled artisan, methods of synthesizing the compounds of the formulae herein will be evident to those of ordinary skill in the art. The synthesized compounds can be separated from a reaction mixture and further purified by a method such as column chromatography, high pressure liquid chromatography, or recrystallization. Additionally, the various synthetic steps may be performed in an alternate sequence or order  
 20 to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 2d. Ed., John Wiley and Sons (1991); L.  
 25 Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and

Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), and subsequent editions thereof.

### **Ribose Replacement Monomer Subunits**

5 iRNA agents can be modified in a number of ways which can optimize one or more characteristics of the iRNA agent. In one aspect, the invention features a ribose replacement monomer subunit (RRMS), or a an iRNA agent which incorporates a RRMS, such as those described herein and those described in one or more of United States Provisional Application Serial No. 60/493,986 (Attorney Docket No. 14174-079P01), filed on August 8, 2003, which  
10 is hereby incorporated by reference; United States Provisional Application Serial No. 60/494,597 (Attorney Docket No. 14174-080P01), filed on August 11, 2003, which is hereby incorporated by reference; United States Provisional Application Serial No. 60/506,341 (Attorney Docket No. 14174-080P02), filed on September 26, 2003, which is hereby incorporated by reference; and in United States Provisional Application Serial No.  
15 60/158,453 (Attorney Docket No. 14174-080P03), filed on November 7, 2003, which is hereby incorporated by reference.

In addition, the invention includes iRNA agents having a RRMS and another element described herein. E.g., the invention includes an iRNA agent described herein, e.g., a palindromic iRNA agent, an iRNA agent having a non canonical pairing, an iRNA agent  
20 which targets a gene described herein, e.g., a gene active in the liver, an iRNA agent having an architecture or structure described herein, an iRNA associated with an amphipathic delivery agent described herein, an iRNA associated with a drug delivery module described herein, an iRNA agent administered as described herein, or an iRNA agent formulated as described herein, which also incorporates a RRMS.

25 The ribose sugar of one or more ribonucleotide subunits of an iRNA agent can be replaced with another moiety, e.g., a non-carbohydrate (preferably cyclic) carrier. A ribonucleotide subunit in which the ribose sugar of the subunit has been so replaced is referred to herein as a ribose replacement modification subunit (RRMS). A cyclic carrier may be a carbocyclic ring system, i.e., all ring atoms are carbon atoms, or a heterocyclic ring  
30 system, i.e., one or more ring atoms may be a heteroatom, e.g., nitrogen, oxygen, sulfur. The cyclic carrier may be a monocyclic ring system, or may contain two or more rings, e.g. fused

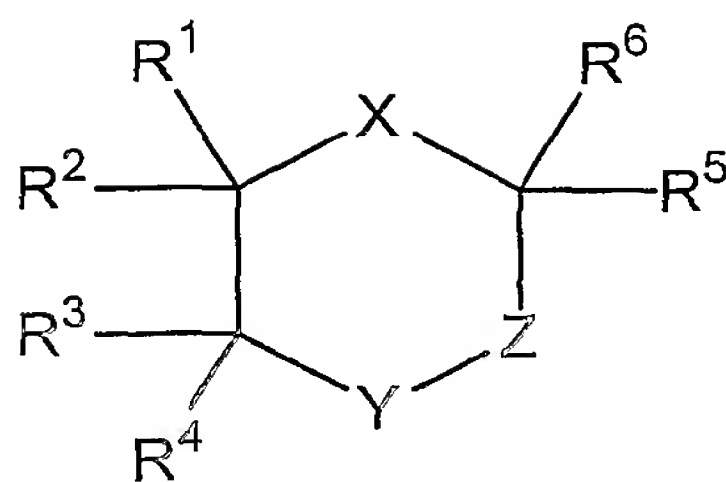


rings. The cyclic carrier may be a fully saturated ring system, or it may contain one or more double bonds.

The carriers further include (i) at least two “backbone attachment points” and (ii) at least one “tethering attachment point.” A “backbone attachment point” as used herein refers to a functional group, e.g. a hydroxyl group, or generally, a bond available for, and that is suitable for incorporation of the carrier into the backbone, e.g., the phosphate, or modified phosphate, e.g., sulfur containing, backbone, of a ribonucleic acid. A “tethering attachment point” as used herein refers to a constituent ring atom of the cyclic carrier, e.g., a carbon atom or a heteroatom (distinct from an atom which provides a backbone attachment point), that connects a selected moiety. The moiety can be, e.g., a ligand, e.g., a targeting or delivery moiety, or a moiety which alters a physical property, e.g., lipophilicity, of an iRNA agent. Optionally, the selected moiety is connected by an intervening tether to the cyclic carrier. Thus, it will include a functional group, e.g., an amino group, or generally, provide a bond, that is suitable for incorporation or tethering of another chemical entity, e.g., a ligand to the constituent ring.

Incorporation of one or more RRMSs described herein into an RNA agent, e.g., an iRNA agent, particularly when tethered to an appropriate entity, can confer one or more new properties to the RNA agent and/or alter, enhance or modulate one or more existing properties in the RNA molecule. E.g., it can alter one or more of lipophilicity or nuclease resistance. Incorporation of one or more RRMSs described herein into an iRNA agent can, particularly when the RRMS is tethered to an appropriate entity, modulate, e.g., increase, binding affinity of an iRNA agent to a target mRNA, change the geometry of the duplex form of the iRNA agent, alter distribution or target the iRNA agent to a particular part of the body, or modify the interaction with nucleic acid binding proteins (e.g., during RISC formation and strand separation).

Accordingly, in one aspect, the invention features, an iRNA agent preferably comprising a first strand and a second strand, wherein at least one subunit having a formula (R-1) is incorporated into at least one of said strands.



(R-1)

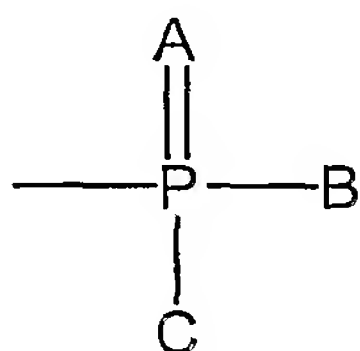
Referring to formula (R-1), X is  $\text{N}(\text{CO})\text{R}^7$ ,  $\text{NR}^7$  or  $\text{CH}_2$ ; Y is  $\text{NR}^8$ , O, S,  $\text{CR}^9\text{R}^{10}$ , or  
 5 absent; and Z is  $\text{CR}^{11}\text{R}^{12}$  or absent.

Each of  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^9$ , and  $\text{R}^{10}$  is, independently, H,  $\text{OR}^a$ ,  $\text{OR}^b$ ,  $(\text{CH}_2)_n\text{OR}^a$ , or  
 $(\text{CH}_2)_n\text{OR}^b$ , provided that at least one of  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^9$ , and  $\text{R}^{10}$  is  $\text{OR}^a$  or  $\text{OR}^b$  and that at  
 least one of  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^9$ , and  $\text{R}^{10}$  is  $(\text{CH}_2)_n\text{OR}^a$ , or  $(\text{CH}_2)_n\text{OR}^b$  (when the RRMS is  
 terminal, one of  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^9$ , and  $\text{R}^{10}$  will include  $\text{R}^a$  and one will include  $\text{R}^b$ ; when the  
 10 RRMS is internal, two of  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^9$ , and  $\text{R}^{10}$  will each include an  $\text{R}^b$ ); further  
 provided that preferably  $\text{OR}^a$  may only be present with  $(\text{CH}_2)_n\text{OR}^b$  and  $(\text{CH}_2)_n\text{OR}^a$  may only  
 be present with  $\text{OR}^b$ .

Each of  $\text{R}^5$ ,  $\text{R}^6$ ,  $\text{R}^{11}$ , and  $\text{R}^{12}$  is, independently, H,  $\text{C}_1\text{-C}_6$  alkyl optionally substituted  
 with 1-3  $\text{R}^{13}$ , or  $\text{C}(\text{O})\text{NHR}^7$ ; or  $\text{R}^5$  and  $\text{R}^{11}$  together are  $\text{C}_3\text{-C}_8$  cycloalkyl optionally  
 15 substituted with  $\text{R}^{14}$ .

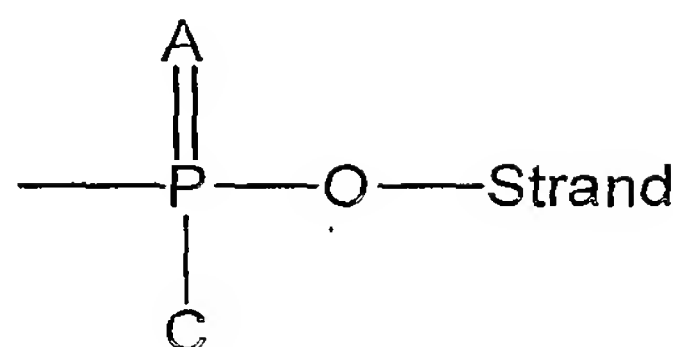
$\text{R}^7$  is  $\text{C}_1\text{-C}_{20}$  alkyl substituted with  $\text{NR}^c\text{R}^d$ ;  $\text{R}^8$  is  $\text{C}_1\text{-C}_6$  alkyl;  $\text{R}^{13}$  is hydroxy,  $\text{C}_1\text{-C}_4$   
 alkoxy, or halo; and  $\text{R}^{14}$  is  $\text{NR}^c\text{R}^7$ .

$\text{R}^a$  is:



; and

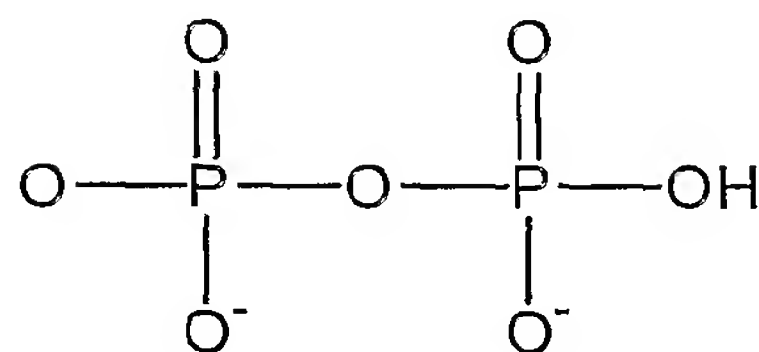
$\text{R}^b$  is:



Each of A and C is, independently, O or S.

B is OH, O<sup>-</sup>, or

5



R<sup>c</sup> is H or C1-C6 alkyl; R<sup>d</sup> is H or a ligand; and n is 1-4.

In a preferred embodiment the ribose is replaced with a pyrroline scaffold, and X is N(CO)R<sup>7</sup> or NR<sup>7</sup>, Y is CR<sup>9</sup>R<sup>10</sup>, and Z is absent.

10 In other preferred embodiments the ribose is replaced with a piperidine scaffold, and X is N(CO)R<sup>7</sup> or NR<sup>7</sup>, Y is CR<sup>9</sup>R<sup>10</sup>, and Z is CR<sup>11</sup>R<sup>12</sup>.

In other preferred embodiments the ribose is replaced with a piperazine scaffold, and X is N(CO)R<sup>7</sup> or NR<sup>7</sup>, Y is NR<sup>8</sup>, and Z is CR<sup>11</sup>R<sup>12</sup>.

15 In other preferred embodiments the ribose is replaced with a morpholino scaffold, and X is N(CO)R<sup>7</sup> or NR<sup>7</sup>, Y is O, and Z is CR<sup>11</sup>R<sup>12</sup>.

In other preferred embodiments the ribose is replaced with a decalin scaffold, and X is CH<sub>2</sub>; Y is CR<sup>9</sup>R<sup>10</sup>; and Z is CR<sup>11</sup>R<sup>12</sup>; and R<sup>5</sup> and R<sup>11</sup> together are C<sup>6</sup> cycloalkyl.

In other preferred embodiments the ribose is replaced with a decalin/indane scaffold and , and X is CH<sub>2</sub>; Y is CR<sup>9</sup>R<sup>10</sup>; and Z is CR<sup>11</sup>R<sup>12</sup>; and R<sup>5</sup> and R<sup>11</sup> together are C<sup>5</sup>  
20 cycloalkyl.

In other preferred embodiments, the ribose is replaced with a hydroxyproline scaffold.

RRMSs described herein may be incorporated into any double-stranded RNA-like molecule described herein, e.g., an iRNA agent. An iRNA agent may include a duplex

comprising a hybridized sense and antisense strand, in which the antisense strand and/or the sense strand may include one or more of the RRMSs described herein. An RRMS can be introduced at one or more points in one or both strands of a double-stranded iRNA agent. An RRMS can be placed at or near (within 1, 2, or 3 positions) of the 3' or 5' end of the sense strand or at near (within 2 or 3 positions of) the 3' end of the antisense strand. In some embodiments it is preferred to not have an RRMS at or near (within 1, 2, or 3 positions of) the 5' end of the antisense strand. An RRMS can be internal, and will preferably be positioned in regions not critical for antisense binding to the target.

In an embodiment, an iRNA agent may have an RRMS at (or within 1, 2, or 3 positions of) the 3' end of the antisense strand. In an embodiment, an iRNA agent may have an RRMS at (or within 1, 2, or 3 positions of) the 3' end of the antisense strand and at (or within 1, 2, or 3 positions of) the 3' end of the sense strand. In an embodiment, an iRNA agent may have an RRMS at (or within 1, 2, or 3 positions of) the 3' end of the antisense strand and an RRMS at the 5' end of the sense strand, in which both ligands are located at the same end of the iRNA agent.

In certain embodiments, two ligands are tethered, preferably, one on each strand and are hydrophobic moieties. While not wishing to be bound by theory, it is believed that pairing of the hydrophobic ligands can stabilize the iRNA agent *via* intermolecular van der Waals interactions.

In an embodiment, an iRNA agent may have an RRMS at (or within 1, 2, or 3 positions of) the 3' end of the antisense strand and an RRMS at the 5' end of the sense strand, in which both RRMSs may share the same ligand (e.g., cholic acid) via connection of their individual tethers to separate positions on the ligand. A ligand shared between two proximal RRMSs is referred to herein as a "hairpin ligand."

In other embodiments, an iRNA agent may have an RRMS at the 3' end of the sense strand and an RRMS at an internal position of the sense strand. An iRNA agent may have an RRMS at an internal position of the sense strand; or may have an RRMS at an internal position of the antisense strand; or may have an RRMS at an internal position of the sense strand and an RRMS at an internal position of the antisense strand.

In preferred embodiments the iRNA agent includes a first and second sequences, which are preferably two separate molecules as opposed to two sequences located on the

same strand, have sufficient complementarity to each other to hybridize (and thereby form a duplex region), e.g., under physiological conditions, e.g., under physiological conditions but not in contact with a helicase or other unwinding enzyme.

It is preferred that the first and second sequences be chosen such that the ds iRNA agent includes a single strand or unpaired region at one or both ends of the molecule. Thus, a ds iRNA agent contains first and second sequences, preferable paired to contain an overhang, e.g., one or two 5' or 3' overhangs but preferably a 3' overhang of 2-3 nucleotides. Most embodiments will have a 3' overhang. Preferred sRNA agents will have single-stranded overhangs, preferably 3' overhangs, of 1 or preferably 2 or 3 nucleotides in length at each end. The overhangs can be the result of one strand being longer than the other, or the result of two strands of the same length being staggered. 5' ends are preferably phosphorylated.

An RNA agent, e.g., an iRNA agent, containing a preferred, but nonlimiting RRMS is presented as formula (R-2) in FIG. 4. The carrier includes two "backbone attachment points" (hydroxyl groups), a "tethering attachment point," and a ligand, which is connected indirectly to the carrier via an intervening tether. The RRMS may be the 5' or 3' terminal subunit of the RNA molecule, i.e., one of the two "W" groups may be a hydroxyl group, and the other "W" group may be a chain of two or more unmodified or modified ribonucleotides. Alternatively, the RRMS may occupy an internal position, and both "W" groups may be one or more unmodified or modified ribonucleotides. More than one RRMS may be present in a RNA molecule, e.g., an iRNA agent.

The modified RNA molecule of formula (R-2) can be obtained using oligonucleotide synthetic methods known in the art. In a preferred embodiment, the modified RNA molecule of formula (II) can be prepared by incorporating one or more of the corresponding RRMS monomer compounds (RRMS monomers, see, e.g., A, B, and C in FIG. 4) into a growing sense or antisense strand, utilizing, e.g., phosphoramidite or H-phosphonate coupling strategies.

The RRMS monomers generally include two differently functionalized hydroxyl groups ( $\text{OFG}^1$  and  $\text{OFG}^2$  above), which are linked to the carrier molecule (see A in FIG. 4), and a tethering attachment point. As used herein, the term "functionalized hydroxyl group" means that the hydroxyl proton has been replaced by another substituent. As shown in representative structures B and C, one hydroxyl group ( $\text{OFG}^1$ ) on the carrier is functionalized



with a protecting group (PG). The other hydroxyl group (OFG<sup>2</sup>) can be functionalized with either (1) a liquid or solid phase synthesis support reagent (solid circle) directly or indirectly through a linker, L, as in **B**, or (2) a phosphorus-containing moiety, e.g., a phosphoramidite as in **C**. The tethering attachment point may be connected to a hydrogen atom, a tether, or a  
5 tethered ligand at the time that the monomer is incorporated into the growing sense or antisense strand (see **R** in Scheme 1). Thus, the tethered ligand can be, but need not be attached to the monomer at the time that the monomer is incorporated into the growing strand. In certain embodiments, the tether, the ligand or the tethered ligand may be linked to a "precursor" RRMS after a "precursor" RRMS monomer has been incorporated into the  
10 strand.

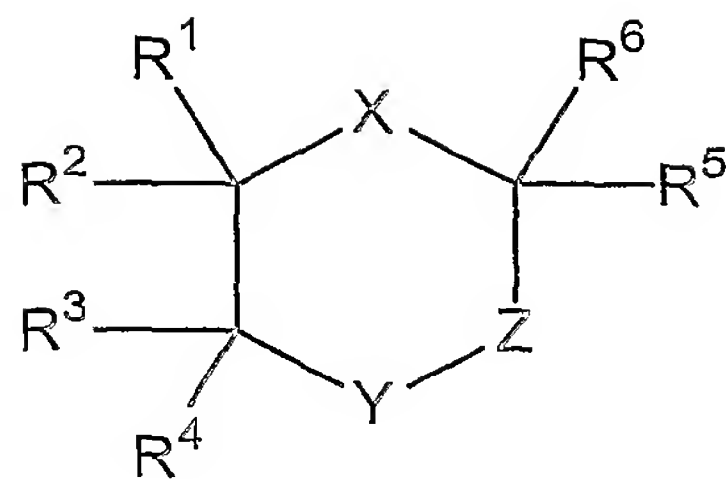
The (OFG<sup>1</sup>) protecting group may be selected as desired, e.g., from T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 2d. Ed., John Wiley and Sons (1991). The protecting group is preferably stable under amidite synthesis conditions, storage conditions, and oligonucleotide synthesis conditions. Hydroxyl groups, -OH, are  
15 nucleophilic groups (i.e., Lewis bases), which react through the oxygen with electrophiles (i.e., Lewis acids). Hydroxyl groups in which the hydrogen has been replaced with a protecting group, e.g., a triarylmethyl group or a trialkylsilyl group, are essentially unreactive as nucleophiles in displacement reactions. Thus, the protected hydroxyl group is useful in preventing e.g., homocoupling of compounds exemplified by structure **C** during  
20 oligonucleotide synthesis. A preferred protecting group is the dimethoxytrityl group.

When the OFG<sup>2</sup> in **B** includes a linker, e.g., a long organic linker, connected to a soluble or insoluble support reagent, solution or solid phase synthesis techniques can be employed to build up a chain of natural and/or modified ribonucleotides once OFG<sup>1</sup> is deprotected and free to react as a nucleophile with another nucleoside or monomer  
25 containing an electrophilic group (e.g., an amidite group). Alternatively, a natural or modified ribonucleotide or oligoribonucleotide chain can be coupled to monomer **C** via an amidite group or H-phosphonate group at OFG<sup>2</sup>. Subsequent to this operation, OFG<sup>1</sup> can be deblocked, and the restored nucleophilic hydroxyl group can react with another nucleoside or monomer containing an electrophilic group (see FIG. 1). R' can be substituted or  
30 unsubstituted alkyl or alkenyl. In preferred embodiments, R' is methyl, allyl or 2-

cyanoethyl. R'' may a C<sub>1</sub>-C<sub>10</sub> alkyl group, preferably it is a branched group containing three or more carbons, e.g., isopropyl.

OFG<sup>2</sup> in **B** can be hydroxyl functionalized with a linker, which in turn contains a liquid or solid phase synthesis support reagent at the other linker terminus. The support  
 5 reagent can be any support medium that can support the monomers described herein. The monomer can be attached to an insoluble support via a linker, L, which allows the monomer (and the growing chain) to be solubilized in the solvent in which the support is placed. The solubilized, yet immobilized, monomer can react with reagents in the surrounding solvent; unreacted reagents and soluble by-products can be readily washed away from the solid  
 10 support to which the monomer or monomer-derived products is attached. Alternatively, the monomer can be attached to a soluble support moiety, e.g., polyethylene glycol (PEG) and liquid phase synthesis techniques can be used to build up the chain. Linker and support medium selection is within skill of the art. Generally the linker may be -C(O)(CH<sub>2</sub>)<sub>q</sub>C(O)-, or -C(O)(CH<sub>2</sub>)<sub>q</sub>S-, preferably, it is oxalyl, succinyl or thioglycolyl. Standard control pore  
 15 glass solid phase synthesis supports can not be used in conjunction with fluoride labile 5' silyl protecting groups because the glass is degraded by fluoride with a significant reduction in the amount of full-length product. Fluoride-stable polystyrene based supports or PEG are preferred.

Preferred carriers have the general formula (R-3) provided below. (In that structure  
 20 preferred backbone attachment points can be chosen from R<sup>1</sup> or R<sup>2</sup>; R<sup>3</sup> or R<sup>4</sup>; or R<sup>9</sup> and R<sup>10</sup> if Y is CR<sup>9</sup>R<sup>10</sup> (two positions are chosen to give two backbone attachment points, e.g., R<sup>1</sup> and R<sup>4</sup>, or R<sup>4</sup> and R<sup>9</sup>. Preferred tethering attachment points include R<sup>7</sup>; R<sup>5</sup> or R<sup>6</sup> when X is CH<sub>2</sub>. The carriers are described below as an entity, which can be incorporated into a strand. Thus, it is understood that the structures also encompass the situations wherein one (in the case of a  
 25 terminal position) or two (in the case of an internal position) of the attachment points, e.g., R<sup>1</sup> or R<sup>2</sup>; R<sup>3</sup> or R<sup>4</sup>; or R<sup>9</sup> or R<sup>10</sup> (when Y is CR<sup>9</sup>R<sup>10</sup>), is connected to the phosphate, or modified phosphate, e.g., sulfur containing, backbone. E.g., one of the above-named R groups can be -CH<sub>2</sub>-, wherein one bond is connected to the carrier and one to a backbone atom, e.g., a linking oxygen or a central phosphorus atom.)



(R-3)

5

X is  $\text{N}(\text{CO})\text{R}^7$ ,  $\text{NR}^7$  or  $\text{CH}_2$ ; Y is  $\text{NR}^8$ , O, S,  $\text{CR}^9\text{R}^{10}$ ; and Z is  $\text{CR}^{11}\text{R}^{12}$  or absent.

Each of  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^9$ , and  $\text{R}^{10}$  is, independently, H,  $\text{OR}^a$ , or  $(\text{CH}_2)_n\text{OR}^b$ , provided that at least two of  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^9$ , and  $\text{R}^{10}$  are  $\text{OR}^a$  and/or  $(\text{CH}_2)_n\text{OR}^b$ .

Each of  $\text{R}^5$ ,  $\text{R}^6$ ,  $\text{R}^{11}$ , and  $\text{R}^{12}$  is, independently, a ligand, H,  $\text{C}_1$ - $\text{C}_6$  alkyl optionally substituted with 1-3  $\text{R}^{13}$ , or  $\text{C}(\text{O})\text{NHR}^7$ ; or  $\text{R}^5$  and  $\text{R}^{11}$  together are  $\text{C}_3$ - $\text{C}_8$  cycloalkyl optionally substituted with  $\text{R}^{14}$ .

$\text{R}^7$  is H, a ligand, or  $\text{C}_1$ - $\text{C}_{20}$  alkyl substituted with  $\text{NR}^c\text{R}^d$ ;  $\text{R}^8$  is H or  $\text{C}_1$ - $\text{C}_6$  alkyl;  $\text{R}^{13}$  is hydroxy,  $\text{C}_1$ - $\text{C}_4$  alkoxy, or halo;  $\text{R}^{14}$  is  $\text{NR}^c\text{R}^7$ ;  $\text{R}^{15}$  is  $\text{C}_1$ - $\text{C}_6$  alkyl optionally substituted with cyano, or  $\text{C}_2$ - $\text{C}_6$  alkenyl;  $\text{R}^{16}$  is  $\text{C}_1$ - $\text{C}_{10}$  alkyl; and  $\text{R}^{17}$  is a liquid or solid phase support reagent.

15

L is  $-\text{C}(\text{O})(\text{CH}_2)_q\text{C}(\text{O})-$ , or  $-\text{C}(\text{O})(\text{CH}_2)_q\text{S}-$ ;  $\text{R}^a$  is  $\text{CAr}_3$ ;  $\text{R}^b$  is  $\text{P}(\text{O})(\text{O}^-)\text{H}$ ,  $\text{P}(\text{OR}^{15})\text{N}(\text{R}^{16})_2$  or  $\text{L}-\text{R}^{17}$ ;  $\text{R}^c$  is H or  $\text{C}_1$ - $\text{C}_6$  alkyl; and  $\text{R}^d$  is H or a ligand.

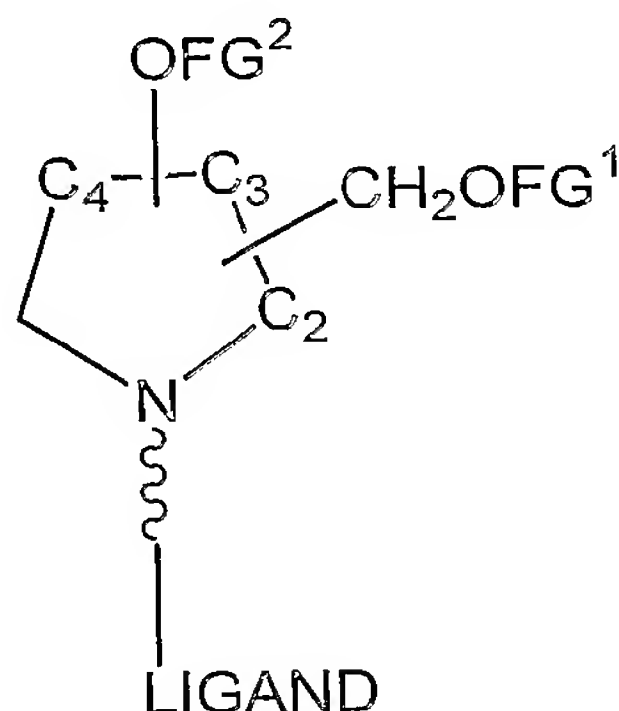
Each Ar is, independently,  $\text{C}_6$ - $\text{C}_{10}$  aryl optionally substituted with  $\text{C}_1$ - $\text{C}_4$  alkoxy; n is 1-4; and q is 0-4.

20

Exemplary carriers include those in which, e.g., X is  $\text{N}(\text{CO})\text{R}^7$  or  $\text{NR}^7$ , Y is  $\text{CR}^9\text{R}^{10}$ , and Z is absent; or X is  $\text{N}(\text{CO})\text{R}^7$  or  $\text{NR}^7$ , Y is  $\text{CR}^9\text{R}^{10}$ , and Z is  $\text{CR}^{11}\text{R}^{12}$ ; or X is  $\text{N}(\text{CO})\text{R}^7$  or  $\text{NR}^7$ , Y is  $\text{NR}^8$ , and Z is  $\text{CR}^{11}\text{R}^{12}$ ; or X is  $\text{N}(\text{CO})\text{R}^7$  or  $\text{NR}^7$ , Y is O, and Z is  $\text{CR}^{11}\text{R}^{12}$ ; or X is  $\text{CH}_2$ ; Y is  $\text{CR}^9\text{R}^{10}$ ; Z is  $\text{CR}^{11}\text{R}^{12}$ , and  $\text{R}^5$  and  $\text{R}^{11}$  together form  $\text{C}_6$  cycloalkyl ( $\text{H}$ ,  $z = 2$ ), or the indane ring system, e.g., X is  $\text{CH}_2$ ; Y is  $\text{CR}^9\text{R}^{10}$ ; Z is  $\text{CR}^{11}\text{R}^{12}$ , and  $\text{R}^5$  and  $\text{R}^{11}$  together form  $\text{C}_5$  cycloalkyl ( $\text{H}$ ,  $z = 1$ ).

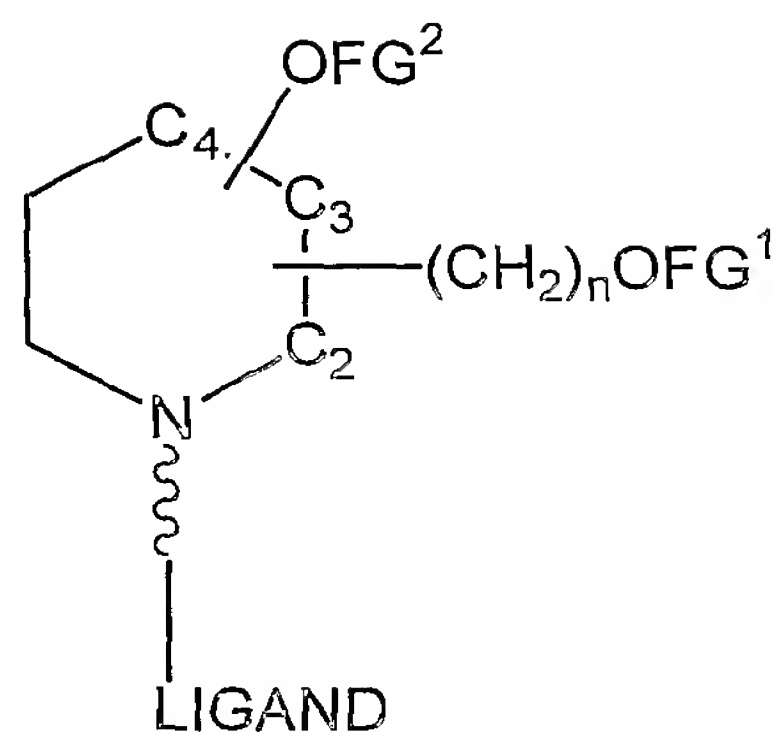
25

In certain embodiments, the carrier may be based on the pyrroline ring system or the 3-hydroxyproline ring system, e.g., X is  $N(CO)R^7$  or  $NR^7$ , Y is  $CR^9R^{10}$ , and Z is absent (**D**).  $OFG^1$  is preferably attached to a primary carbon, e.g., an exocyclic alkylene

**D**

5 group, e.g., a methylene group, connected to one of the carbons in the five-membered ring ( $-CH_2OFG^1$  in **D**).  $OFG^2$  is preferably attached directly to one of the carbons in the five-membered ring ( $-OFG^2$  in **D**). For the pyrroline-based carriers,  $-CH_2OFG^1$  may be attached to C-2 and  $OFG^2$  may be attached to C-3; or  $-CH_2OFG^1$  may be attached to C-3 and  $OFG^2$  may be attached to C-4. . In certain embodiments,  $CH_2OFG^1$  and  $OFG^2$  may be geminally substituted to one of the above-referenced carbons. For the 3-hydroxyproline-based carriers,  $-CH_2OFG^1$  may be attached to C-2 and  $OFG^2$  may be attached to C-4. The pyrroline- and 3-hydroxyproline-based monomers may therefore contain linkages (e.g., carbon-carbon bonds) wherein bond rotation is restricted about that particular linkage, e.g. restriction resulting from the presence of a ring. Thus,  $CH_2OFG^1$  and  $OFG^2$  may be *cis* or *trans* with respect to one another in any of the pairings delineated above. Accordingly, all *cis/trans* isomers are expressly included. The monomers may also contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of the monomers are expressly included. The tethering attachment point is preferably nitrogen.

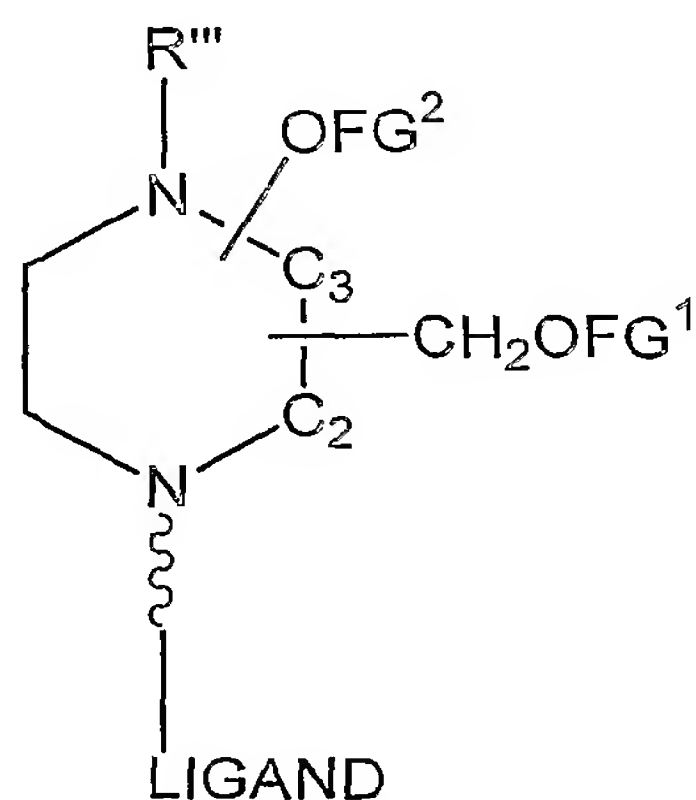
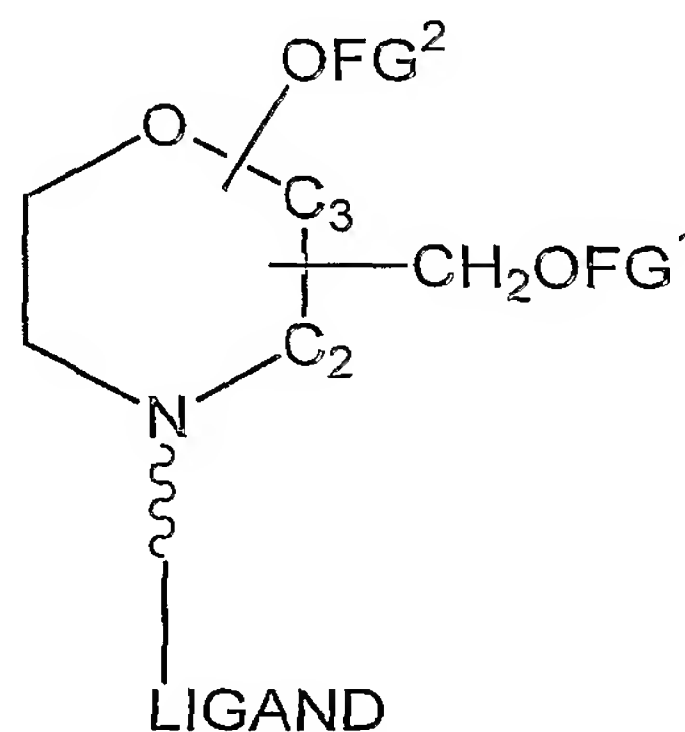
20 In certain embodiments, the carrier may be based on the piperidine ring system (**E**), e.g., X is  $N(CO)R^7$  or  $NR^7$ , Y is  $CR^9R^{10}$ , and Z is  $CR^{11}R^{12}$ .  $OFG^1$  is preferably

**E**

attached to a primary carbon, e.g., an exocyclic alkylene group, e.g., a methylene group ( $n=1$ ) or ethylene group ( $n=2$ ), connected to one of the carbons in the six-membered ring [ $-(CH_2)_nOFG^1$  in **E**].  $OFG^2$  is preferably attached directly to one of the carbons in the six-membered ring ( $-OFG^2$  in **E**).  $-(CH_2)_nOFG^1$  and  $OFG^2$  may be disposed in a geminal manner on the ring, i.e., both groups may be attached to the same carbon, e.g., at C-2, C-3, or C-4. Alternatively,  $-(CH_2)_nOFG^1$  and  $OFG^2$  may be disposed in a vicinal manner on the ring, i.e., both groups may be attached to adjacent ring carbon atoms, e.g.,  $-(CH_2)_nOFG^1$  may be attached to C-2 and  $OFG^2$  may be attached to C-3;  $-(CH_2)_nOFG^1$  may be attached to C-3 and  $OFG^2$  may be attached to C-2;  $-(CH_2)_nOFG^1$  may be attached to C-3 and  $OFG^2$  may be attached to C-4; or  $-(CH_2)_nOFG^1$  may be attached to C-4 and  $OFG^2$  may be attached to C-3. The piperidine-based monomers may therefore contain linkages (e.g., carbon-carbon bonds) wherein bond rotation is restricted about that particular linkage, e.g. restriction resulting from the presence of a ring. Thus,  $-(CH_2)_nOFG^1$  and  $OFG^2$  may be *cis* or *trans* with respect to one another in any of the pairings delineated above. Accordingly, all *cis/trans* isomers are expressly included. The monomers may also contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of the monomers are expressly included. The tethering attachment point is preferably nitrogen.



In certain embodiments, the carrier may be based on the piperazine ring system (**F**), e.g., X is N(CO)R<sup>7</sup> or NR<sup>7</sup>, Y is NR<sup>8</sup>, and Z is CR<sup>11</sup>R<sup>12</sup>, or the morpholine ring system (**G**), e.g., X is N(CO)R<sup>7</sup> or NR<sup>7</sup>, Y is O, and Z is CR<sup>11</sup>R<sup>12</sup>. OFG<sup>1</sup> is preferably

**F****G**

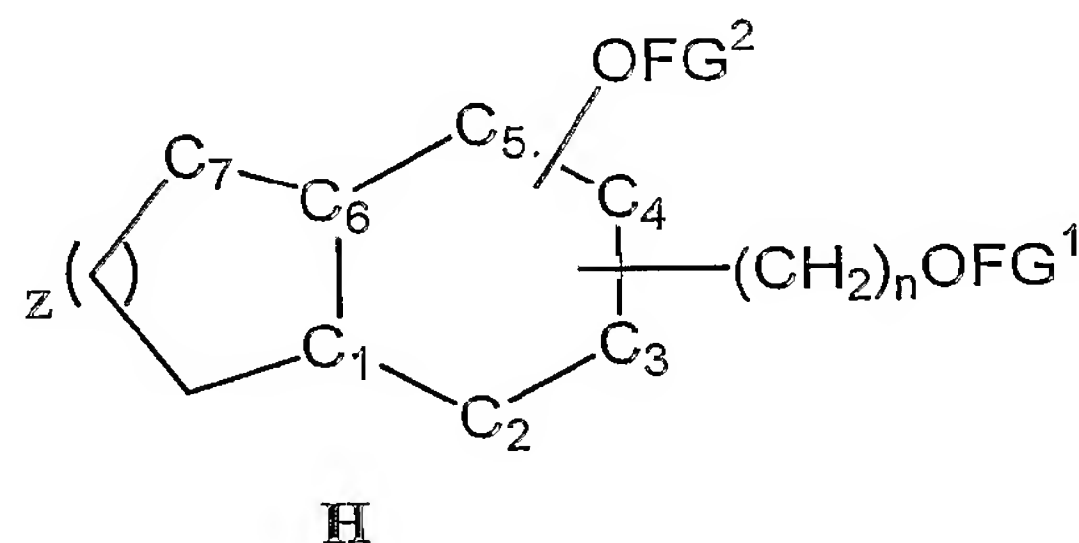
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attached to a primary carbon, e.g., an exocyclic alkylene group, e.g., a methylene group, connected to one of the carbons in the six-membered ring (-CH<sub>2</sub>OFG<sup>1</sup> in **F** or **G**). OFG<sup>2</sup> is preferably attached directly to one of the carbons in the six-membered rings (-OFG<sup>2</sup> in **F** or **G**). For both **F** and **G**, -CH<sub>2</sub>OFG<sup>1</sup> may be attached to C-2 and OFG<sup>2</sup> may be attached to C-3; or *vice versa*. In certain embodiments, CH<sub>2</sub>OFG<sup>1</sup> and OFG<sup>2</sup> may be geminally substituted to one of the above-referenced carbons. The piperazine- and morpholine-based monomers may therefore contain linkages (e.g., carbon-carbon bonds) wherein bond rotation is restricted about that particular linkage, e.g. restriction resulting from the presence of a ring. Thus, CH<sub>2</sub>OFG<sup>1</sup> and OFG<sup>2</sup> may be *cis* or *trans* with respect to one another in any of the pairings delineated above. Accordingly, all *cis/trans* isomers are expressly included. The monomers may also contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of the monomers are expressly included. R''' can be, e.g., C<sub>1</sub>-C<sub>6</sub> alkyl, preferably CH<sub>3</sub>. The tethering attachment point is preferably nitrogen in both **F** and **G**.

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In certain embodiments, the carrier may be based on the decalin ring system, e.g., X is CH<sub>2</sub>; Y is CR<sup>9</sup>R<sup>10</sup>; Z is CR<sup>11</sup>R<sup>12</sup>, and R<sup>5</sup> and R<sup>11</sup> together form C<sub>6</sub> cycloalkyl (**H**, z = 2), or the indane ring system, e.g., X is CH<sub>2</sub>; Y is CR<sup>9</sup>R<sup>10</sup>; Z is CR<sup>11</sup>R<sup>12</sup>, and R<sup>5</sup> and R<sup>11</sup> together form C<sub>5</sub> cycloalkyl (**H**, z = 1). OFG<sup>1</sup> is preferably attached to a primary carbon,

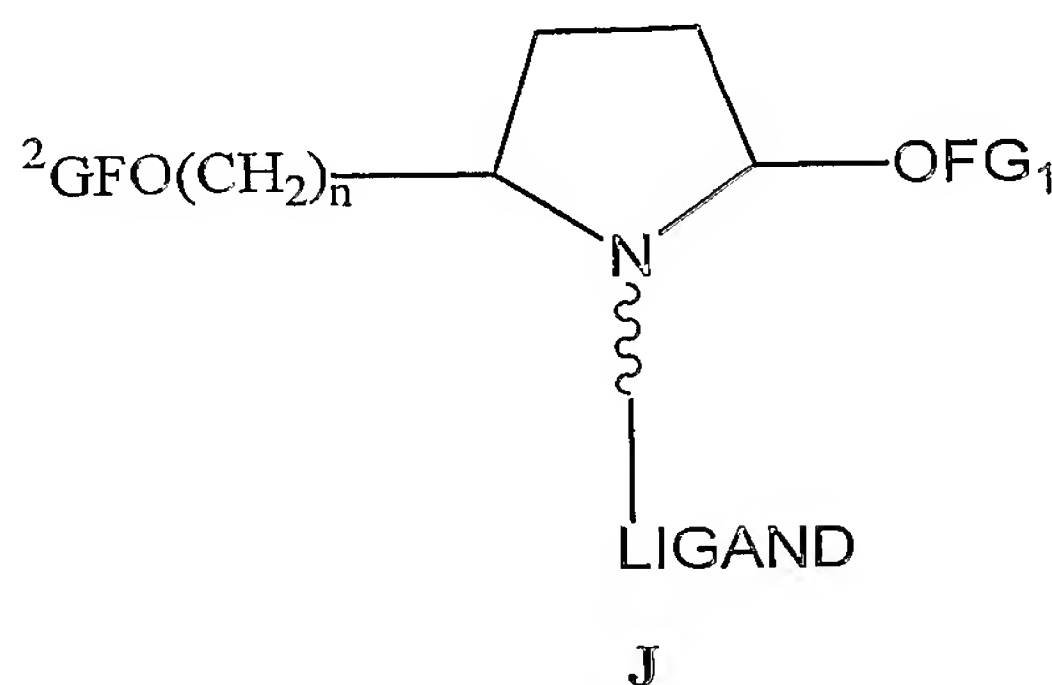
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e.g., an exocyclic methylene group (n=1) or ethylene group (n=2) connected to one of C-2, C-3, C-4, or C-5 [-(CH<sub>2</sub>)<sub>n</sub>OFG<sup>1</sup> in **H**]. OFG<sup>2</sup> is preferably attached directly to one of C-2, C-3, C-4, or C-5 (-OFG<sup>2</sup> in **H**). -(CH<sub>2</sub>)<sub>n</sub>OFG<sup>1</sup> and OFG<sup>2</sup> may be disposed in a geminal manner on the ring, i.e., both groups may be attached to the same carbon, e.g., at C-2, C-3, C-4, or C-5. Alternatively, -(CH<sub>2</sub>)<sub>n</sub>OFG<sup>1</sup> and OFG<sup>2</sup> may be disposed in a vicinal manner on the ring, i.e., both groups may be attached to adjacent ring carbon atoms, e.g., -(CH<sub>2</sub>)<sub>n</sub>OFG<sup>1</sup> may be attached to C-2 and OFG<sup>2</sup> may be attached to C-3; -(CH<sub>2</sub>)<sub>n</sub>OFG<sup>1</sup> may be attached to C-3 and OFG<sup>2</sup> may be attached to C-2; -(CH<sub>2</sub>)<sub>n</sub>OFG<sup>1</sup> may be attached to C-3 and OFG<sup>2</sup> may be attached to C-4; or -(CH<sub>2</sub>)<sub>n</sub>OFG<sup>1</sup> may be attached to C-4 and OFG<sup>2</sup> may be attached to C-3; -(CH<sub>2</sub>)<sub>n</sub>OFG<sup>1</sup> may be attached to C-4 and OFG<sup>2</sup> may be attached to C-5; or -(CH<sub>2</sub>)<sub>n</sub>OFG<sup>1</sup> may be attached to C-5 and OFG<sup>2</sup> may be attached to C-4. The decalin or indane-based monomers may therefore contain linkages (e.g., carbon-carbon bonds) wherein bond rotation is restricted about that particular linkage, e.g. restriction resulting from the presence of a ring. Thus, -(CH<sub>2</sub>)<sub>n</sub>OFG<sup>1</sup> and OFG<sup>2</sup> may be *cis* or *trans* with respect to one another in any of the pairings delineated above. Accordingly, all *cis/trans* isomers are expressly included. The monomers may also contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of the monomers are expressly included. In a preferred embodiment, the substituents at C-1 and C-6 are *trans* with respect to one another. The tethering attachment point is preferably C-6 or C-7.

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Other carriers may include those based on 3-hydroxyproline (J). Thus,  $-(CH_2)_nOFG^1$  and  $OFG^2$  may be *cis* or *trans* with respect to one another. Accordingly, all *cis/trans* isomers are expressly included. The monomers may also contain one or more asymmetric centers



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and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of the monomers are expressly included. The tethering attachment point is preferably nitrogen.

Representative carriers are shown in FIG. 5.

10 In certain embodiments, a moiety, e.g., a ligand may be connected indirectly to the carrier *via* the intermediacy of an intervening tether. Tethers are connected to the carrier at the tethering attachment point (TAP) and may include any  $C_1$ - $C_{100}$  carbon-containing moiety, (e.g.  $C_1$ - $C_{75}$ ,  $C_1$ - $C_{50}$ ,  $C_1$ - $C_{20}$ ,  $C_1$ - $C_{10}$ ,  $C_1$ - $C_6$ ), preferably having at least one nitrogen atom. In preferred embodiments, the nitrogen atom forms part of a terminal amino group on the tether,

15 which may serve as a connection point for the ligand. Preferred tethers (underlined) include  $TAP-(CH_2)_nNH_2$ ;  $TAP-C(O)(CH_2)_nNH_2$ ; or  $TAP-NR^{''''}(CH_2)_nNH_2$ , in which  $n$  is 1-6 and  $R^{''''}$  is  $C_1$ - $C_6$  alkyl, and  $R^d$  is hydrogen or a ligand. In other embodiments, the nitrogen may form part of a terminal oxyamino group, e.g.,  $-ONH_2$ , or hydrazino group,  $-NHNH_2$ . The tether may optionally be substituted, e.g., with hydroxy, alkoxy, perhaloalkyl, and/or

20 optionally inserted with one or more additional heteroatoms, e.g., N, O, or S. Preferred tethered ligands may include, e.g.,  $TAP-(CH_2)_nNH(LIGAND)$ ,  $TAP-C(O)(CH_2)_nNH(LIGAND)$ , or  $TAP-NR^{''''}(CH_2)_nNH(LIGAND)$ ;  $TAP-(CH_2)_nONH(LIGAND)$ ,  $TAP-C(O)(CH_2)_nONH(LIGAND)$ , or  $TAP-NR^{''''}(CH_2)_nONH(LIGAND)$ ;  $TAP-(CH_2)_nNHNH_2(LIGAND)$ ,  $TAP-C(O)(CH_2)_nNHNH_2(LIGAND)$ , or  $TAP-NR^{''''}(CH_2)_nNHNH_2(LIGAND)$ .

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In other embodiments the tether may include an electrophilic moiety, preferably at the terminal position of the tether. Preferred electrophilic moieties include, e.g., an aldehyde, alkyl halide, mesylate, tosylate, nosylate, or brosylate, or an activated carboxylic acid ester, e.g. an NHS ester, or a pentafluorophenyl ester. Preferred tethers (underlined) include TAP-  
 5 (CH<sub>2</sub>)<sub>n</sub>CHO; TAP-C(O)(CH<sub>2</sub>)<sub>n</sub>CHO; or TAP-NR<sup>'''</sup>(CH<sub>2</sub>)<sub>n</sub>CHO, in which n is 1-6 and R<sup>'''</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl; or TAP-(CH<sub>2</sub>)<sub>n</sub>C(O)ONHS; TAP-C(O)(CH<sub>2</sub>)<sub>n</sub>C(O)ONHS; or TAP-NR<sup>'''</sup>(CH<sub>2</sub>)<sub>n</sub>C(O)ONHS, in which n is 1-6 and R<sup>'''</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl; TAP-(CH<sub>2</sub>)<sub>n</sub>C(O)OC<sub>6</sub>F<sub>5</sub>; TAP-C(O)(CH<sub>2</sub>)<sub>n</sub>C(O)OC<sub>6</sub>F<sub>5</sub>; or TAP-NR<sup>'''</sup>(CH<sub>2</sub>)<sub>n</sub>C(O)OC<sub>6</sub>F<sub>5</sub>, in which n is 1-6 and R<sup>'''</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl; or -(CH<sub>2</sub>)<sub>n</sub>CH<sub>2</sub>LG; TAP-C(O)(CH<sub>2</sub>)<sub>n</sub>CH<sub>2</sub>LG; or  
 10 TAP-NR<sup>'''</sup>(CH<sub>2</sub>)<sub>n</sub>CH<sub>2</sub>LG, in which n is 1-6 and R<sup>'''</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl (LG can be a leaving group, e.g., halide, mesylate, tosylate, nosylate, brosylate). Tethering can be carried out by coupling a nucleophilic group of a ligand, e.g., a thiol or amino group with an electrophilic group on the tether.

#### 15 *Tethered Entities*

A wide variety of entities can be tethered to an iRNA agent, e.g., to the carrier of an RRMS. Examples are described below in the context of an RRMS but that is only preferred, entities can be coupled at other points to an iRNA agent.

Preferred moieties are ligands, which are coupled, preferably covalently, either  
 20 directly or indirectly via an intervening tether, to the RRMS carrier. In preferred embodiments, the ligand is attached to the carrier *via* an intervening tether. As discussed above, the ligand or tethered ligand may be present on the RRMS monomer when the RRMS monomer is incorporated into the growing strand. In some embodiments, the ligand may be incorporated into a "precursor" RRMS after a "precursor" RRMS monomer has been  
 25 incorporated into the growing strand. For example, an RRMS monomer having, e.g., an amino-terminated tether (i.e., having no associated ligand), e.g., TAP-(CH<sub>2</sub>)<sub>n</sub>NH<sub>2</sub> may be incorporated into a growing sense or antisense strand. In a subsequent operation, i.e., after incorporation of the precursor monomer into the strand, a ligand having an electrophilic group, e.g., a pentafluorophenyl ester or aldehyde group, can subsequently be attached to the  
 30 precursor RRMS by coupling the electrophilic group of the ligand with the terminal nucleophilic group of the precursor RRMS tether.

In preferred embodiments, a ligand alters the distribution, targeting or lifetime of an iRNA agent into which it is incorporated. In preferred embodiments a ligand provides an enhanced affinity for a selected target, e.g, molecule, cell or cell type, compartment, e.g., a cellular or organ compartment, tissue, organ or region of the body, as, e.g., compared to a species absent such a ligand. Preferred ligands will not take part in duplex pairing in a duplexed nucleic acid.

Preferred ligands can improve transport, hybridization, and specificity properties and may also improve nuclease resistance of the resultant natural or modified oligoribonucleotide, or a polymeric molecule comprising any combination of monomers described herein and/or natural or modified ribonucleotides.

Ligands in general can include therapeutic modifiers, e.g., for enhancing uptake; diagnostic compounds or reporter groups e.g., for monitoring distribution; cross-linking agents; and nuclease-resistance conferring moieties. General examples include lipids, steroids, vitamins, sugars, proteins, peptides, polyamines, and peptide mimics.

Ligands can include a naturally occurring substance, such as a protein (e.g., human serum albumin (HSA), low-density lipoprotein (LDL), or globulin); carbohydrate (e.g., a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin or hyaluronic acid); or a lipid. The ligand may also be a recombinant or synthetic molecule, such as a synthetic polymer, e.g., a synthetic polyamino acid. Examples of polyamino acids include polyamino acid is a polylysine (PLL), poly L-aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolide) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacrylic acid), N-isopropylacrylamide polymers, or polyphosphazene. Example of polyamines include: polyethylenimine, polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or an alpha helical peptide.

Ligands can also include targeting groups, e.g., a cell or tissue targeting agent, e.g., a lectin, glycoprotein, lipid or protein, e.g., an antibody, that binds to a specified cell type such as a cancer cell, endothelial cell, bone cell. A targeting group can be a thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, Mucin carbohydrate, multivalent



lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-gulucosamine multivalent mannose, multivalent fucose, glycosylated polyaminoacids, multivalent galactose, transferrin, bisphosphonate, polyglutamate, polyaspartate, a lipid, cholesterol, a steroid, bile acid, folate, vitamin B12, biotin, or an RGD peptide or RGD peptide mimetic.

5 Other examples of ligands include dyes, intercalating agents (*e.g.* acridines), cross-linkers (*e.g.* psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (*e.g.*, phenazine, dihydrophenazine), artificial endonucleases (*e.g.* EDTA), lipophilic molecules, *e.g.*, cholesterol, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, 10 geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine) and peptide conjugates (*e.g.*, antennapedia peptide, Tat peptide), alkylating agents, phosphate, amino, mercapto, PEG (*e.g.*, PEG-40K), MPEG, [MPEG]<sub>2</sub>, polyamino, alkyl, substituted alkyl, radiolabeled markers, enzymes, haptens (*e.g.* 15 biotin), transport/absorption facilitators (*e.g.*, aspirin, vitamin E, folic acid), synthetic ribonucleases (*e.g.*, imidazole, bisimidazole, histamine, imidazole clusters, acridine-imidazole conjugates, Eu<sup>3+</sup> complexes of tetraazamacrocycles), dinitrophenyl, HRP, or AP.

Ligands can be proteins, *e.g.*, glycoproteins, or peptides, *e.g.*, molecules having a specific affinity for a co-ligand, or antibodies *e.g.*, an antibody, that binds to a specified cell 20 type such as a cancer cell, endothelial cell, or bone cell. Ligands may also include hormones and hormone receptors. They can also include non-peptidic species, such as lipids, lectins, carbohydrates, vitamins, cofactors, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-gulucosamine multivalent mannose, or multivalent fucose. The ligand can be, for example, a lipopolysaccharide, an activator of p38 MAP kinase, or an 25 activator of NF- $\kappa$ B.

The ligand can be a substance, *e.g.*, a drug, which can increase the uptake of the iRNA agent into the cell, for example, by disrupting the cell's cytoskeleton, *e.g.*, by disrupting the cell's microtubules, microfilaments, and/or intermediate filaments. The drug can be, for example, taxon, vincristine, vinblastine, cytochalasin, nocodazole, japlakinolide, latrunculin 30 A, phalloidin, swinholide A, indanocine, or myoservin.

The ligand can increase the uptake of the iRNA agent into the cell by activating an inflammatory response, for example. Exemplary ligands that would have such an effect include tumor necrosis factor alpha (TNFalpha), interleukin-1 beta, or gamma interferon.

In one aspect, the ligand is a lipid or lipid-based molecule. Such a lipid or lipid-based molecule preferably binds a serum protein, e.g., human serum albumin (HSA). An HSA binding ligand allows for distribution of the conjugate to a target tissue, e.g., a non-kidney target tissue of the body. Preferably, the target tissue is the liver, preferably parenchymal cells of the liver. Other molecules that can bind HSA can also be used as ligands. For example, neproxin or aspirin can be used. A lipid or lipid-based ligand can (a) increase resistance to degradation of the conjugate, (b) increase targeting or transport into a target cell or cell membrane, and/or (c) can be used to adjust binding to a serum protein, e.g., HSA.

A lipid based ligand can be used to modulate, e.g., control the binding of the conjugate to a target tissue. For example, a lipid or lipid-based ligand that binds to HSA more strongly will be less likely to be targeted to the kidney and therefore less likely to be cleared from the body. A lipid or lipid-based ligand that binds to HSA less strongly can be used to target the conjugate to the kidney.

In a preferred embodiment, the lipid based ligand binds HSA. Preferably, it binds HSA with a sufficient affinity such that the conjugate will be preferably distributed to a non-kidney tissue. However, it is preferred that the affinity not be so strong that the HSA-ligand binding cannot be reversed.

In another preferred embodiment, the lipid based ligand binds HSA weakly or not at all, such that the conjugate will be preferably distributed to the kidney. Other moieties that target to kidney cells can also be used in place of or in addition to the lipid based ligand.

In another aspect, the ligand is a moiety, e.g., a vitamin, which is taken up by a target cell, e.g., a proliferating cell. These are particularly useful for treating disorders characterized by unwanted cell proliferation, e.g., of the malignant or non-malignant type, e.g., cancer cells. Exemplary vitamins include vitamin A, E, and K. Other exemplary vitamins include are B vitamin, e.g., folic acid, B12, riboflavin, biotin, pyridoxal or other vitamins or nutrients taken up by cancer cells. Also included are HSA and low density lipoprotein (LDL).

In another aspect, the ligand is a cell-permeation agent, preferably a helical cell-permeation agent. Preferably, the agent is amphipathic. An exemplary agent is a peptide such as tat or antennopodia. If the agent is a peptide, it can be modified, including a peptidylmimetic, invertomers, non-peptide or pseudo-peptide linkages, and use of D-amino  
5 acids. The helical agent is preferably an alpha-helical agent, which preferably has a lipophilic and a lipophobic phase.

The ligand can be a peptide or peptidomimetic. A peptidomimetic (also referred to herein as an oligopeptidomimetic) is a molecule capable of folding into a defined three-dimensional structure similar to a natural peptide. The attachment of peptide and  
10 peptidomimetics to iRNA agents can affect pharmacokinetic distribution of the iRNA, such as by enhancing cellular recognition and absorption. The peptide or peptidomimetic moiety can be about 5-50 amino acids long, *e.g.*, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acids long (see Table 1, for example).

**Table 1.** Exemplary Cell Permeation Peptides

Cell Permeation Peptide	Amino acid Sequence	Reference
Penetratin	RQIKIWFQNRRMKWKK (SEQ ID NO:6737)	Derossi <i>et al.</i> , J. Biol. Chem. 269:10444, 1994
Tat fragment (48-60)	GRKKRRQRRRPPQC (SEQ ID NO:6738)	Vives <i>et al.</i> , J. Biol. Chem., 272:16010, 1997
Signal Sequence-based peptide	GALFLGWLGAAGSTMGAWSQPKKKRKV (SEQ ID NO:6738)	Chaloin <i>et al.</i> , Biochem. Biophys. Res. Commun., 243:601, 1998
PVEC	LLIILRRRIRKQAHASK (SEQ ID NO:6739)	Elmqvist <i>et al.</i> , Exp. Cell Res., 269:237, 2001
Transportan	GWTLNSAGYLLKINLKALAALAKKIL (SEQ ID NO:6740)	Pooga <i>et al.</i> , FASEB J., 12:67, 1998
Amphiphilic model peptide	KLALKLALKALKAALKLA (SEQ ID NO:6741)	Oehlke <i>et al.</i> , Mol. Ther., 2:339, 2000
Arg <sub>9</sub>	RRRRRRRRR (SEQ ID NO:6742)	Mitchell <i>et al.</i> , J. Pept. Res., 56:318, 2000
Bacterial cell wall permeating	KFFKFFKFFK (SEQ ID NO:6743)	
LL-37	LLGDFFRKSKEKIGKEFKRIVQRIKDFLRN LVPRTES (SEQ ID NO:6744)	
Cecropin P1	SWLSKTAKKLENSAKKRISGIAIAIQGGP R (SEQ ID NO:6745)	
$\alpha$ -defensin	ACYCRIPACIAGERRYGTCTIYQGRLWAFCC (SEQ ID NO:6746)	
b-defensin	DHYNCVSSGGQCLYSACPIFTKIQTGTCYR GKAKCCK (SEQ ID NO:6747)	
Bactenecin	RKCRIVVIRVCR (SEQ ID NO:6748)	
PR-39	RRRPRPPYLPRPRPPFPFPPRLPPRIPPGFPP RFPPRFPGKR-NH <sub>2</sub> (SEQ ID NO:6749)	
Indolicidin	ILPWKWPWWPWRR-NH <sub>2</sub> (SEQ ID NO:6750)	

A peptide or peptidomimetic can be, for example, a cell permeation peptide, cationic peptide, amphipathic peptide, or hydrophobic peptide (*e.g.*, consisting primarily of Tyr, Trp or Phe). The peptide moiety can be a dendrimer peptide, constrained peptide or crosslinked

peptide. In another alternative, the peptide moiety can include a hydrophobic membrane translocation sequence (MTS). An exemplary hydrophobic MTS-containing peptide is RFGF having the amino acid sequence AAVALLPAVLLALLAP (SEQ ID NO:6751). An RFGF analogue (*e.g.*, amino acid sequence AALLPVLLAAP (SEQ ID NO:6752))  
5 containing a hydrophobic MTS can also be a targeting moiety. The peptide moiety can be a “delivery” peptide, which can carry large polar molecules including peptides, oligonucleotides, and protein across cell membranes. For example, sequences from the HIV Tat protein (GRKKRRQRRRPPQ (SEQ ID NO:6753)) and the Drosophila Antennapedia protein (RQIKIWFQNRRMKWKK (SEQ ID NO:6754)) have been found to be capable of  
10 functioning as delivery peptides. A peptide or peptidomimetic can be encoded by a random sequence of DNA, such as a peptide identified from a phage-display library, or one-bead-one-compound (OBOC) combinatorial library (Lam *et al.*, Nature, 354:82-84, 1991). Preferably the peptide or peptidomimetic tethered to an iRNA agent via an incorporated monomer unit is a cell targeting peptide such as an arginine-glycine-aspartic acid (RGD)-  
15 peptide, or RGD mimic. A peptide moiety can range in length from about 5 amino acids to about 40 amino acids. The peptide moieties can have a structural modification, such as to increase stability or direct conformational properties. Any of the structural modifications described below can be utilized.

An RGD peptide moiety can be used to target a tumor cell, such as an endothelial  
20 tumor cell or a breast cancer tumor cell (Zitzmann *et al.*, Cancer Res., 62:5139-43, 2002). An RGD peptide can facilitate targeting of an iRNA agent to tumors of a variety of other tissues, including the lung, kidney, spleen, or liver (Aoki *et al.*, Cancer Gene Therapy 8:783-787, 2001). The RGD peptide can be linear or cyclic, and can be modified, *e.g.*, glycosylated or methylated to facilitate targeting to specific tissues. For example, a glycosylated RGD  
25 peptide can deliver an iRNA agent to a tumor cell expressing  $\alpha_v\beta_3$  (Haubner *et al.*, Jour. Nucl. Med., 42:326-336, 2001).

Peptides that target markers enriched in proliferating cells can be used. *E.g.*, RGD containing peptides and peptidomimetics can target cancer cells, in particular cells that exhibit an  $\alpha_v\beta_3$  integrin. Thus, one could use RGD peptides, cyclic peptides containing  
30 RGD, RGD peptides that include D-amino acids, as well as synthetic RGD mimics. In addition to RGD, one can use other moieties that target the  $\alpha_v\beta_3$  integrin ligand. Generally,



such ligands can be used to control proliferating cells and angiogenesis. Preferred conjugates of this type include an iRNA agent that targets PECAM-1, VEGF, or other cancer gene, e.g., a cancer gene described herein.

A "cell permeation peptide" is capable of permeating a cell, e.g., a microbial cell, such as a bacterial or fungal cell, or a mammalian cell, such as a human cell. A microbial cell-permeating peptide can be, for example, an  $\alpha$ -helical linear peptide (e.g., LL-37 or Ceropin P1), a disulfide bond-containing peptide (e.g.,  $\alpha$ -defensin,  $\beta$ -defensin or bactenecin), or a peptide containing only one or two dominating amino acids (e.g., PR-39 or indolicidin). A cell permeation peptide can also include a nuclear localization signal (NLS). For example, a cell permeation peptide can be a bipartite amphipathic peptide, such as MPG, which is derived from the fusion peptide domain of HIV-1 gp41 and the NLS of SV40 large T antigen (Simeoni *et al.*, Nucl. Acids Res. 31:2717-2724, 2003).

In one embodiment, a targeting peptide tethered to an RRMS can be an amphipathic  $\alpha$ -helical peptide. Exemplary amphipathic  $\alpha$ -helical peptides include, but are not limited to, cecropins, lycotoxins, paradaxins, buforin, CPF, bombinin-like peptide (BLP), cathelicidins, ceratotoxins, *S. clava* peptides, hagfish intestinal antimicrobial peptides (HFIAPs), magainines, brevinins-2, dermaseptins, melittins, pleurocidin, H<sub>2</sub>A peptides, Xenopus peptides, esculentins-1, and caerins. A number of factors will preferably be considered to maintain the integrity of helix stability. For example, a maximum number of helix stabilization residues will be utilized (e.g., leu, ala, or lys), and a minimum number helix destabilization residues will be utilized (e.g., proline, or cyclic monomeric units. The capping residue will be considered (for example Gly is an exemplary N-capping residue and/or C-terminal amidation can be used to provide an extra H-bond to stabilize the helix. Formation of salt bridges between residues with opposite charges, separated by  $i \pm 3$ , or  $i \pm 4$  positions can provide stability. For example, cationic residues such as lysine, arginine, homo-arginine, ornithine or histidine can form salt bridges with the anionic residues glutamate or aspartate.

Peptide and peptidomimetic ligands include those having naturally occurring or modified peptides, e.g., D or L peptides;  $\alpha$ ,  $\beta$ , or  $\gamma$  peptides; N-methyl peptides; azapeptides; peptides having one or more amide, i.e., peptide, linkages replaced with one or more urea, thiourea, carbamate, or sulfonyl urea linkages; or cyclic peptides.

*Methods for making iRNA agents*

iRNA agents can include modified or non-naturally occurring bases, e.g., bases described in copending and coowned United States Provisional Application Serial No. 60/463,772 (Attorney Docket No. 14174-070P01), filed on April 17, 2003, which is hereby  
5 incorporated by reference and/or in copending and coowned United States Provisional Application Serial No. 60/465,802 (Attorney Docket No. 14174-074P01), filed on April 25, 2003, which is hereby incorporated by reference. Monomers and iRNA agents which include such bases can be made by the methods found in United States Provisional Application Serial  
10 No. 60/463,772 (Attorney Docket No. 14174-070P01), filed on April 17, 2003, and/or in United States Provisional Application Serial No. 60/465,802 (Attorney Docket No. 14174-074P01), filed on April 25, 2003.

In addition, the invention includes iRNA agents having a modified or non-naturally occurring base and another element described herein. E.g., the invention includes an iRNA  
15 agent described herein, e.g., a palindromic iRNA agent, an iRNA agent having a non canonical pairing, an iRNA agent which targets a gene described herein, e.g., a gene active in the liver, an iRNA agent having an architecture or structure described herein, an iRNA associated with an amphipathic delivery agent described herein, an iRNA associated with a drug delivery module described herein, an iRNA agent administered as described herein, or  
20 an iRNA agent formulated as described herein, which also incorporates a modified or non-naturally occurring base.

The synthesis and purification of oligonucleotide peptide conjugates can be performed by established methods. See, for example, Trufert *et al.*, Tetrahedron, 52:3005, 1996; and Manoharan, "Oligonucleotide Conjugates in Antisense Technology," in Antisense  
25 Drug Technology, ed. S.T. Crooke, Marcel Dekker, Inc., 2001.

In one embodiment of the invention, a peptidomimetic can be modified to create a constrained peptide that adopts a distinct and specific preferred conformation, which can increase the potency and selectivity of the peptide. For example, the constrained peptide can be an azapeptide (Gante, Synthesis, 405-413, 1989). An azapeptide is synthesized by  
30 replacing the  $\alpha$ -carbon of an amino acid with a nitrogen atom without changing the structure of the amino acid side chain. For example, the azapeptide can be synthesized by using

hydrazine in traditional peptide synthesis coupling methods, such as by reacting hydrazine with a "carbonyl donor," e.g., phenylchloroformate.

In one embodiment of the invention, a peptide or peptidomimetic (e.g., a peptide or peptidomimetic tethered to an RRMS) can be an N-methyl peptide. N-methyl peptides are composed of N-methyl amino acids, which provide an additional methyl group in the peptide backbone, thereby potentially providing additional means of resistance to proteolytic cleavage. N-methyl peptides can be synthesized by methods known in the art (see, for example, Lindgren *et al.*, Trends Pharmacol. Sci. 21:99, 2000; Cell Penetrating Peptides: Processes and Applications, Langel, ed., CRC Press, Boca Raton, FL, 2002; Fische *et al.*, Bioconjugate. Chem. 12: 825, 2001; Wander *et al.*, J. Am. Chem. Soc., 124:13382, 2002). For example, an Ant or Tat peptide can be an N-methyl peptide.

In one embodiment of the invention, a peptide or peptidomimetic (e.g., a peptide or peptidomimetic tethered to an RRMS) can be a  $\beta$ -peptide.  $\beta$ -peptides form stable secondary structures such as helices, pleated sheets, turns and hairpins in solutions. Their cyclic derivatives can fold into nanotubes in the solid state.  $\beta$ -peptides are resistant to degradation by proteolytic enzymes.  $\beta$ -peptides can be synthesized by methods known in the art. For example, an Ant or Tat peptide can be a  $\beta$ -peptide.

In one embodiment of the invention, a peptide or peptidomimetic (e.g., a peptide or peptidomimetic tethered to an RRMS) can be an oligocarbamate. Oligocarbamate peptides are internalized into a cell by a transport pathway facilitated by carbamate transporters. For example, an Ant or Tat peptide can be an oligocarbamate.

In one embodiment of the invention, a peptide or peptidomimetic (e.g., a peptide or peptidomimetic tethered to an RRMS) can be an oligourea conjugate (or an oligothiourea conjugate), in which the amide bond of a peptidomimetic is replaced with a urea moiety. Replacement of the amide bond provides increased resistance to degradation by proteolytic enzymes, e.g., proteolytic enzymes in the gastrointestinal tract. In one embodiment, an oligourea conjugate is tethered to an iRNA agent for use in oral delivery. The backbone in each repeating unit of an oligourea peptidomimetic can be extended by one carbon atom in comparison with the natural amino acid. The single carbon atom extension can increase peptide stability and lipophilicity, for example. An oligourea peptide can therefore be advantageous when an iRNA agent is directed for passage through a bacterial cell wall, or

when an iRNA agent must traverse the blood-brain barrier, such as for the treatment of a neurological disorder. In one embodiment, a hydrogen bonding unit is conjugated to the oligoureia peptide, such as to create an increased affinity with a receptor. For example, an Ant or Tat peptide can be an oligoureia conjugate (or an oligothioureia conjugate).

5       The siRNA peptide conjugates of the invention can be affiliated with, *e.g.*, tethered to, RRMSs occurring at various positions on an iRNA agent. For example, a peptide can be terminally conjugated, on either the sense or the antisense strand, or a peptide can be bisconjugated (one peptide tethered to each end, one conjugated to the sense strand, and one conjugated to the antisense strand). In another option, the peptide can be internally  
10       conjugated, such as in the loop of a short hairpin iRNA agent. In yet another option, the peptide can be affiliated with a complex, such as a peptide-carrier complex.

      A peptide-carrier complex consists of at least a carrier molecule, which can encapsulate one or more iRNA agents (such as for delivery to a biological system and/or a cell), and a peptide moiety tethered to the outside of the carrier molecule, such as for  
15       targeting the carrier complex to a particular tissue or cell type. A carrier complex can carry additional targeting molecules on the exterior of the complex, or fusogenic agents to aid in cell delivery. The one or more iRNA agents encapsulated within the carrier can be conjugated to lipophilic molecules, which can aid in the delivery of the agents to the interior of the carrier.

20       A carrier molecule or structure can be, for example, a micelle, a liposome (*e.g.*, a cationic liposome), a nanoparticle, a microsphere, or a biodegradable polymer. A peptide moiety can be tethered to the carrier molecule by a variety of linkages, such as a disulfide linkage, an acid labile linkage, a peptide-based linkage, an oxyamino linkage or a hydrazine linkage. For example, a peptide-based linkage can be a GFLG peptide. Certain linkages will  
25       have particular advantages, and the advantages (or disadvantages) can be considered depending on the tissue target or intended use. For example, peptide based linkages are stable in the blood stream but are susceptible to enzymatic cleavage in the lysosomes.

### *Targeting*

30       The iRNA agents of the invention are particularly useful when targeted to the liver. An iRNA agent can be targeted to the liver by incorporation of an RRMS containing a ligand



that targets the liver. For example, a liver-targeting agent can be a lipophilic moiety. Preferred lipophilic moieties include lipid, cholesterol, oleyl, retinyl, or cholesteryl residues. Other lipophilic moieties that can function as liver-targeting agents include cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-  
5 O(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)chenic acid, dimethoxytrityl, or phenoxazine.

An iRNA agent can also be targeted to the liver by association with a low-density lipoprotein (LDL), such as lactosylated LDL. Polymeric carriers complexed with sugar  
10 residues can also function to target iRNA agents to the liver.

A targeting agent that incorporates a sugar, *e.g.*, galactose and/or analogues thereof, is particularly useful. These agents target, in particular, the parenchymal cells of the liver. For example, a targeting moiety can include more than one or preferably two or three galactose moieties, spaced about 15 angstroms from each other. The targeting moiety can alternatively  
15 be lactose (*e.g.*, three lactose moieties), which is glucose coupled to a galactose. The targeting moiety can also be N-Acetyl-Galactosamine, N-Ac-Glucosamine. A mannose or mannose-6-phosphate targeting moiety can be used for macrophage targeting.

Conjugation of an iRNA agent with a serum albumin (SA), such as human serum albumin, can also be used to target the iRNA agent to the liver.

20 An iRNA agent targeted to the liver by an RRMS targeting moiety described herein can target a gene expressed in the liver. For example, the iRNA agent can target p21(WAF1/DIP1), P27(KIP1), the  $\alpha$ -fetoprotein gene, beta-catenin, or c-MET, such as for treating a cancer of the liver. In another embodiment, the iRNA agent can target apoB-100, such as for the treatment of an HDL/LDL cholesterol imbalance; dyslipidemias, *e.g.*, familial  
25 combined hyperlipidemia (FCHL), or acquired hyperlipidemia; hypercholesterolemia; statin-resistant hypercholesterolemia; coronary artery disease (CAD); coronary heart disease (CHD); or atherosclerosis. In another embodiment, the iRNA agent can target forkhead homologue in rhabdomyosarcoma (FKHR); glucagon; glucagon receptor; glycogen phosphorylase; PPAR-Gamma Coactivator (PGC-1); Fructose-1,6-bisphosphatase; glucose-  
30 6-phosphatase; glucose-6-phosphate translocator; glucokinase inhibitory regulatory protein; or phosphoenolpyruvate carboxykinase (PEPCK), such as to inhibit hepatic glucose



production in a mammal, such as a human, such as for the treatment of diabetes. In another embodiment, an iRNA agent targeted to the liver can target Factor V, e.g., the Leiden Factor V allele, such as to reduce the tendency to form a blood clot. An iRNA agent targeted to the liver can include a sequence which targets hepatitis virus (e.g., Hepatitis A, B, C, D, E, F, G, or H). For example, an iRNA agent of the invention can target any one of the nonstructural proteins of HCV: NS3, 4A, 4B, 5A, or 5B. For the treatment of hepatitis B, an iRNA agent can target the protein X (HBx) gene, for example.

Preferred ligands on RRMSs include folic acid, glucose, cholesterol, cholic acid, Vitamin E, Vitamin K, or Vitamin A.

#### 10        Definitions

The term "halo" refers to any radical of fluorine, chlorine, bromine or iodine.

The term "alkyl" refers to a hydrocarbon chain that may be a straight chain or branched chain, containing the indicated number of carbon atoms. For example, C<sub>1</sub>-C<sub>12</sub> alkyl indicates that the group may have from 1 to 12 (inclusive) carbon atoms in it. The term "haloalkyl" refers to an alkyl in which one or more hydrogen atoms are replaced by halo, and includes alkyl moieties in which all hydrogens have been replaced by halo (e.g., perfluoroalkyl). Alkyl and haloalkyl groups may be optionally inserted with O, N, or S. The terms "aralkyl" refers to an alkyl moiety in which an alkyl hydrogen atom is replaced by an aryl group. Aralkyl includes groups in which more than one hydrogen atom has been replaced by an aryl group. Examples of "aralkyl" include benzyl, 9-fluorenyl, benzhydryl, and trityl groups.

The term "alkenyl" refers to a straight or branched hydrocarbon chain containing 2-8 carbon atoms and characterized in having one or more double bonds. Examples of a typical alkenyl include, but not limited to, allyl, propenyl, 2-butenyl, 3-hexenyl and 3-octenyl groups. The term "alkynyl" refers to a straight or branched hydrocarbon chain containing 2-8 carbon atoms and characterized in having one or more triple bonds. Some examples of a typical alkynyl are ethynyl, 2-propynyl, and 3-methylbutynyl, and propargyl. The sp<sup>2</sup> and sp<sup>3</sup> carbons may optionally serve as the point of attachment of the alkenyl and alkynyl groups, respectively.

The term “alkoxy” refers to an -O-alkyl radical. The term “aminoalkyl” refers to an alkyl substituted with an amino group. The term “mercapto” refers to an -SH radical. The term “thioalkoxy” refers to an -S-alkyl radical.

The term “alkylene” refers to a divalent alkyl (*i.e.*, -R-), e.g., -CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-, and -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-. The term “alkylenedioxy” refers to a divalent species of the structure -O-R-O-, in which R represents an alkylene.

The term “aryl” refers to an aromatic monocyclic, bicyclic, or tricyclic hydrocarbon ring system, wherein any ring atom capable of substitution can be substituted by a substituent. Examples of aryl moieties include, but are not limited to, phenyl, naphthyl, and anthracenyl.

The term “cycloalkyl” as employed herein includes saturated cyclic, bicyclic, tricyclic, or polycyclic hydrocarbon groups having 3 to 12 carbons, wherein any ring atom capable of substitution can be substituted by a substituent. The cycloalkyl groups herein described may also contain fused rings. Fused rings are rings that share a common carbon-carbon bond. Examples of cycloalkyl moieties include, but are not limited to, cyclohexyl, adamantyl, and norbornyl.

The term “heterocyclyl” refers to a nonaromatic 3-10 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein any ring atom capable of substitution can be substituted by a substituent. The heterocyclyl groups herein described may also contain fused rings. Fused rings are rings that share a common carbon-carbon bond. Examples of heterocyclyl include, but are not limited to tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholino, pyrrolinyl and pyrrolidinyl.

The term “heteroaryl” refers to an aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein any ring atom capable of substitution can be substituted by a substituent.

The term “oxo” refers to an oxygen atom, which forms a carbonyl when attached to carbon, an N-oxide when attached to nitrogen, and a sulfoxide or sulfone when attached to sulfur.

The term “acyl” refers to an alkylcarbonyl, cycloalkylcarbonyl, arylcarbonyl, heterocyclcarbonyl, or heteroarylcarbonyl substituent, any of which may be further substituted by substituents.

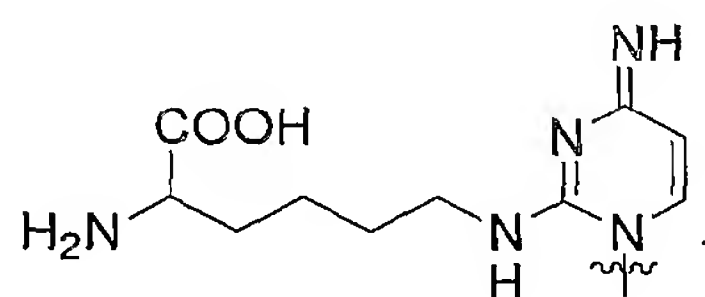
The term "substituents" refers to a group “substituted” on an alkyl, cycloalkyl, alkenyl, alkynyl, heterocycl, heterocycloalkenyl, cycloalkenyl, aryl, or heteroaryl group at any atom of that group. Suitable substituents include, without limitation, alkyl, alkenyl, alkynyl, alkoxy, halo, hydroxy, cyano, nitro, amino, SO<sub>3</sub>H, sulfate, phosphate, perfluoroalkyl, perfluoroalkoxy, methylenedioxy, ethylenedioxy, carboxyl, oxo, thioxo, imino (alkyl, aryl, aralkyl), S(O)<sub>n</sub>alkyl (where n is 0-2), S(O)<sub>n</sub> aryl (where n is 0-2), S(O)<sub>n</sub> heteroaryl (where n is 0-2), S(O)<sub>n</sub> heterocycl (where n is 0-2), amine (mono-, di-, alkyl, cycloalkyl, aralkyl, heteroaralkyl, and combinations thereof), ester (alkyl, aralkyl, heteroaralkyl), amide (mono-, di-, alkyl, aralkyl, heteroaralkyl, and combinations thereof), sulfonamide (mono-, di-, alkyl, aralkyl, heteroaralkyl, and combinations thereof), unsubstituted aryl, unsubstituted heteroaryl, unsubstituted heterocycl, and unsubstituted cycloalkyl. In one aspect, the substituents on a group are independently any one single, or any subset of the aforementioned substituents.

The terms “adeninyl, cytosinyl, guaninyl, thyminyl, and uracil” and the like refer to radicals of adenine, cytosine, guanine, thymine, and uracil.

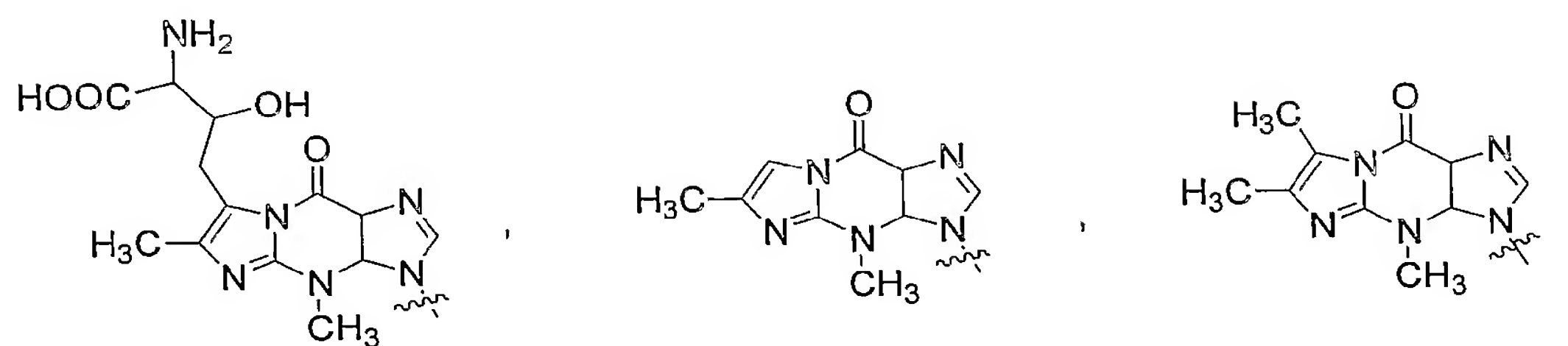
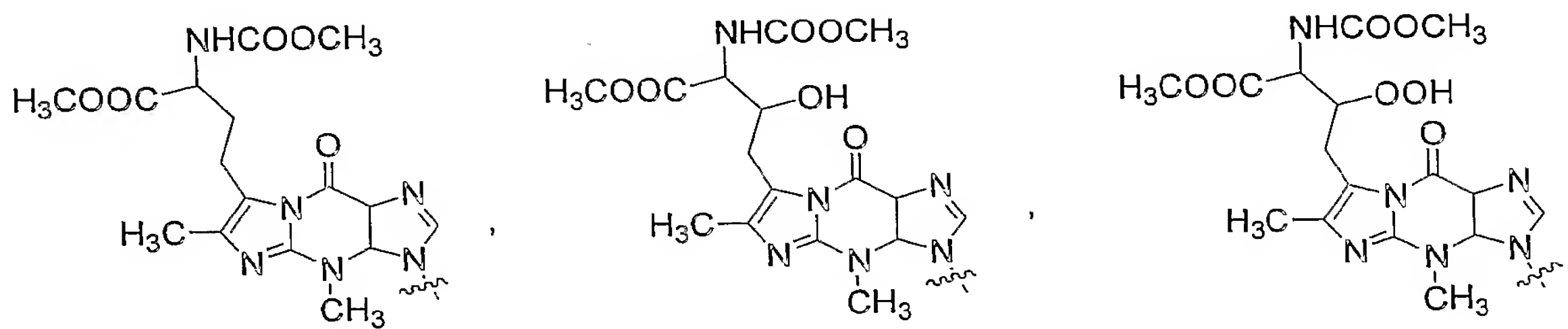
As used herein, an “unusual” nucleobase can include any one of the following:

2-methyladeninyl,  
N6-methyladeninyl,  
2-methylthio-N6-methyladeninyl,  
N6-isopentenyladeninyl,  
2-methylthio-N6-isopentenyladeninyl,  
N6-(cis-hydroxyisopentenyl)adeninyl,  
2-methylthio-N6-(cis-hydroxyisopentenyl) adeninyl,  
N6-glycinylcarbamoyladeninyl,  
N6-threonylcarbamoyladeninyl,

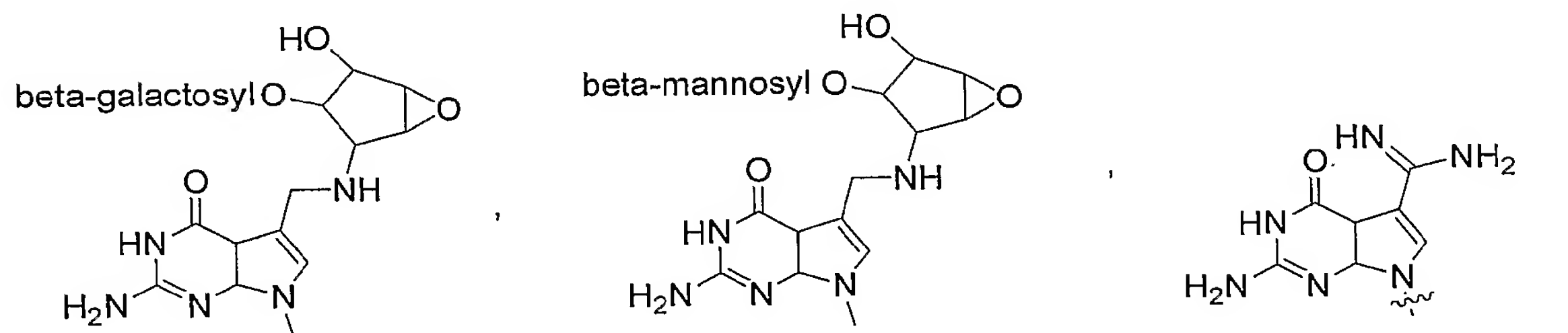
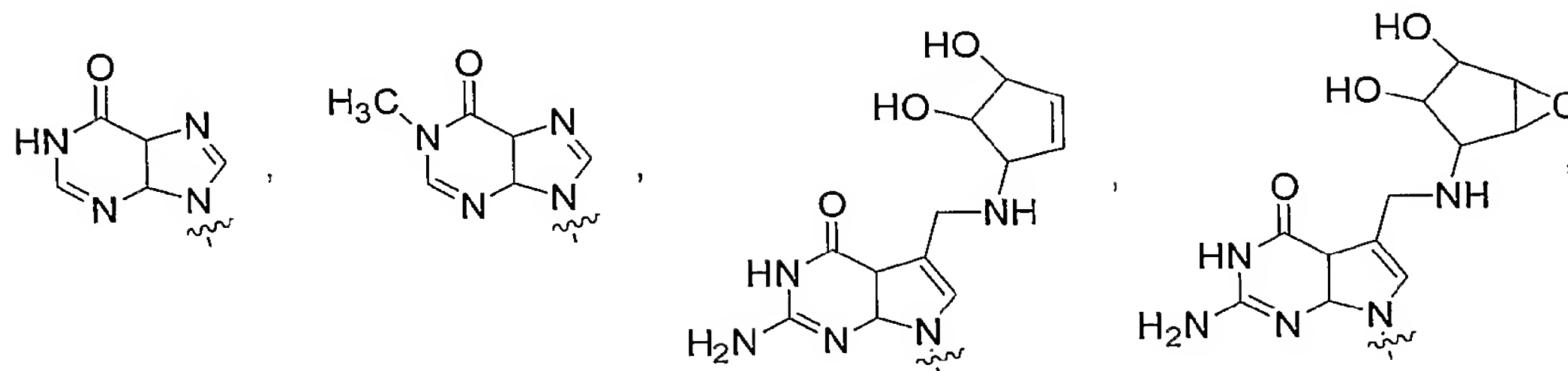
2-methylthio-N6-threonyl carbamoyladeninylyl,  
N6-methyl-N6-threonylcarbamoyladeninylyl,  
N6-hydroxynorvalylcarbamoyladeninylyl,  
2-methylthio-N6-hydroxynorvalyl carbamoyladeninylyl,  
5 N6,N6-dimethyladeninylyl,  
3-methylcytosinylyl,  
5-methylcytosinylyl,  
2-thiocytosinylyl,  
5-formylcytosinylyl,



,  
N4-methylcytosinylyl,  
5-hydroxymethylcytosinylyl,  
15 1-methylguaninylyl,  
N2-methylguaninylyl,  
7-methylguaninylyl,  
N2,N2-dimethylguaninylyl,



N<sup>2</sup>,7-dimethylguaninyl,





N2,N2,7-trimethylguaninyl,  
1-methylguaninyl,  
7-cyano-7-deazaguaninyl,  
5 7-aminomethyl-7-deazaguaninyl,  
pseudouracilyl,  
dihydrouracilyl,  
5-methyluracilyl,  
1-methylpseudouracilyl,  
10 2-thiouracilyl,  
4-thiouracilyl,  
2-thiothyminyl  
5-methyl-2-thiouracilyl,  
3-(3-amino-3-carboxypropyl)uracilyl,  
15 5-hydroxyuracilyl,  
5-methoxyuracilyl,  
uracilyl 5-oxyacetic acid,  
uracilyl 5-oxyacetic acid methyl ester,  
5-(carboxyhydroxymethyl)uracilyl,  
20 5-(carboxyhydroxymethyl)uracilyl methyl ester,  
5-methoxycarbonylmethyluracilyl,  
5-methoxycarbonylmethyl-2-thiouracilyl,  
5-aminomethyl-2-thiouracilyl,  
5-methylaminomethyluracilyl,  
25 5-methylaminomethyl-2-thiouracilyl,  
5-methylaminomethyl-2-selenouracilyl,  
5-carbamoylmethyluracilyl,  
5-carboxymethylaminomethyluracilyl,  
5-carboxymethylaminomethyl-2-thiouracilyl,  
30 3-methyluracilyl,  
1-methyl-3-(3-amino-3-carboxypropyl) pseudouracilyl,

5-carboxymethyluracilyl,  
5-methyldihydrouracilyl, or  
3-methylpseudouracilyl.

5        Asymmetrical Modifications

In one aspect, the invention features an iRNA agent which can be asymmetrically modified as described herein.

In addition, the invention includes iRNA agents having asymmetrical modifications and another element described herein. E.g., the invention includes an iRNA agent described  
10        herein, e.g., a palindromic iRNA agent, an iRNA agent having a non canonical pairing, an iRNA agent which targets a gene described herein, e.g., a gene active in the liver, an iRNA agent having an architecture or structure described herein, an iRNA associated with an amphipathic delivery agent described herein, an iRNA associated with a drug delivery module described herein, an iRNA agent administered as described herein, or an iRNA agent  
15        formulated as described herein, which also incorporates an asymmetrical modification.

iRNA agents of the invention can be asymmetrically modified. An asymmetrically modified iRNA agent is one in which a strand has a modification which is not present on the other strand. An asymmetrical modification is a modification found on one strand but not on the other strand. Any modification, e.g., any modification described herein, can be present as  
20        an asymmetrical modification. An asymmetrical modification can confer any of the desired properties associated with a modification, e.g., those properties discussed herein. E.g., an asymmetrical modification can: confer resistance to degradation, an alteration in half life; target the iRNA agent to a particular target, e.g., to a particular tissue; modulate, e.g., increase or decrease, the affinity of a strand for its complement or target sequence; or hinder  
25        or promote modification of a terminal moiety, e.g., modification by a kinase or other enzymes involved in the RISC mechanism pathway. The designation of a modification as having one property does not mean that it has no other property, e.g., a modification referred to as one which promotes stabilization might also enhance targeting.

While not wishing to be bound by theory or any particular mechanistic model, it is  
30        believed that asymmetrical modification allows an iRNA agent to be optimized in view of the different or "asymmetrical" functions of the sense and antisense strands. For example, both

strands can be modified to increase nuclease resistance, however, since some changes can inhibit RISC activity, these changes can be chosen for the sense strand. In addition, since some modifications, e.g., targeting moieties, can add large bulky groups that, e.g., can interfere with the cleavage activity of the RISC complex, such modifications are preferably placed on the sense strand. Thus, targeting moieties, especially bulky ones (e.g. cholesterol), are preferentially added to the sense strand. In one embodiment, an asymmetrical modification in which a phosphate of the backbone is substituted with S, e.g., a phosphorothioate modification, is present in the antisense strand, and a 2' modification, e.g., 2' OMe is present in the sense strand. A targeting moiety can be present at either (or both) the 5' or 3' end of the sense strand of the iRNA agent. In a preferred example, a P of the backbone is replaced with S in the antisense strand, 2'OMe is present in the sense strand, and a targeting moiety is added to either the 5' or 3' end of the sense strand of the iRNA agent.

In a preferred embodiment an asymmetrically modified iRNA agent has a modification on the sense strand which modification is not found on the antisense strand and the antisense strand has a modification which is not found on the sense strand.

Each strand can include one or more asymmetrical modifications. By way of example: one strand can include a first asymmetrical modification which confers a first property on the iRNA agent and the other strand can have a second asymmetrical modification which confers a second property on the iRNA. E.g., one strand, e.g., the sense strand can have a modification which targets the iRNA agent to a tissue, and the other strand, e.g., the antisense strand, has a modification which promotes hybridization with the target gene sequence.

In some embodiments both strands can be modified to optimize the same property, e.g., to increase resistance to nucleolytic degradation, but different modifications are chosen for the sense and the antisense strands, e.g., because the modifications affect other properties as well. E.g., since some changes can affect RISC activity these modifications are chosen for the sense strand.

In an embodiment one strand has an asymmetrical 2' modification, e.g., a 2' OMe modification, and the other strand has an asymmetrical modification of the phosphate backbone, e.g., a phosphorothioate modification. So, in one embodiment the antisense strand has an asymmetrical 2' OMe modification and the sense strand has an asymmetrical

phosphorothioate modification (or vice versa). In a particularly preferred embodiment the RNAi agent will have asymmetrical 2'-O alkyl, preferably, 2'-OMe modifications on the sense strand and asymmetrical backbone P modification, preferably a phosphothioate modification in the antisense strand. There can be one or multiple 2'-OMe modifications, e.g., at least 2, 3, 4, 5, or 6, of the subunits of the sense strand can be so modified. There can be one or multiple phosphorothioate modifications, e.g., at least 2, 3, 4, 5, or 6, of the subunits of the antisense strand can be so modified. It is preferable to have an iRNA agent wherein there are multiple 2'-OMe modifications on the sense strand and multiple phosphorothioate modifications on the antisense strand. All of the subunits on one or both strands can be so modified. A particularly preferred embodiment of multiple asymmetric modification on both strands has a duplex region about 20-21, and preferably 19, subunits in length and one or two 3' overhangs of about 2 subunits in length.

Asymmetrical modifications are useful for promoting resistance to degradation by nucleases, e.g., endonucleases. iRNA agents can include one or more asymmetrical modifications which promote resistance to degradation. In preferred embodiments the modification on the antisense strand is one which will not interfere with silencing of the target, e.g., one which will not interfere with cleavage of the target. Most if not all sites on a strand are vulnerable, to some degree, to degradation by endonucleases. One can determine sites which are relatively vulnerable and insert asymmetrical modifications which inhibit degradation. It is often desirable to provide asymmetrical modification of a UA site in an iRNA agent, and in some cases it is desirable to provide the UA sequence on both strands with asymmetrical modification. Examples of modifications which inhibit endonucleolytic degradation can be found herein. Particularly favored modifications include: 2' modification, e.g., provision of a 2' OMe moiety on the U, especially on a sense strand; modification of the backbone, e.g., with the replacement of an O with an S, in the phosphate backbone, e.g., the provision of a phosphorothioate modification, on the U or the A or both, especially on an antisense strand; replacement of the U with a C5 amino linker; replacement of the A with a G (sequence changes are preferred to be located on the sense strand and not the antisense strand); and modification of the at the 2', 6', 7', or 8' position. Preferred embodiments are those in which one or more of these modifications are present on the sense

but not the antisense strand, or embodiments where the antisense strand has fewer of such modifications.

Asymmetrical modification can be used to inhibit degradation by exonucleases. Asymmetrical modifications can include those in which only one strand is modified as well  
5 as those in which both are modified. In preferred embodiments the modification on the antisense strand is one which will not interfere with silencing of the target, e.g., one which will not interfere with cleavage of the target. Some embodiments will have an asymmetrical modification on the sense strand, e.g., in a 3' overhang, e.g., at the 3' terminus, and on the antisense strand, e.g., in a 3' overhang, e.g., at the 3' terminus. If the modifications introduce  
10 moieties of different size it is preferable that the larger be on the sense strand. If the modifications introduce moieties of different charge it is preferable that the one with greater charge be on the sense strand.

Examples of modifications which inhibit exonucleolytic degradation can be found herein. Particularly favored modifications include: 2' modification, e.g., provision of a 2'  
15 OMe moiety in a 3' overhang, e.g., at the 3' terminus (3' terminus means at the 3' atom of the molecule or at the most 3' moiety, e.g., the most 3' P or 2' position, as indicated by the context); modification of the backbone, e.g., with the replacement of a P with an S, e.g., the provision of a phosphorothioate modification, or the use of a methylated P in a 3' overhang, e.g., at the 3' terminus; combination of a 2' modification, e.g., provision of a 2' O Me  
20 moiety and modification of the backbone, e.g., with the replacement of a P with an S, e.g., the provision of a phosphorothioate modification, or the use of a methylated P, in a 3' overhang, e.g., at the 3' terminus; modification with a 3' alkyl; modification with an abasic pyrolidine in a 3' overhang, e.g., at the 3' terminus; modification with naproxene, ibuprofen, or other moieties which inhibit degradation at the 3' terminus. Preferred embodiments are  
25 those in which one or more of these modifications are present on the sense but not the antisense strand, or embodiments where the antisense strand has fewer of such modifications.

Modifications, e.g., those described herein, which affect targeting can be provided as asymmetrical modifications. Targeting modifications which can inhibit silencing, e.g., by inhibiting cleavage of a target, can be provided as asymmetrical modifications of the sense  
30 strand. A biodistribution altering moiety, e.g., cholesterol, can be provided in one or more, e.g., two, asymmetrical modifications of the sense strand. Targeting modifications which



introduce moieties having a relatively large molecular weight, e.g., a molecular weight of more than 400, 500, or 1000 daltons, or which introduce a charged moiety (e.g., having more than one positive charge or one negative charge) can be placed on the sense strand.

Modifications, e.g., those described herein, which modulate, e.g., increase or  
5 decrease, the affinity of a strand for its complement or target, can be provided as asymmetrical modifications. These include: 5 methyl U; 5 methyl C; pseudouridine, Locked nucleic acids, 2 thio U and 2-amino-A. In some embodiments one or more of these is provided on the antisense strand.

iRNA agents have a defined structure, with a sense strand and an antisense strand,  
10 and in many cases short single strand overhangs, e.g., of 2 or 3 nucleotides are present at one or both 3' ends. Asymmetrical modification can be used to optimize the activity of such a structure, e.g., by being placed selectively within the iRNA. E.g., the end region of the iRNA agent defined by the 5' end of the sense strand and the 3' end of the antisense strand is important for function. This region can include the terminal 2, 3, or 4 paired nucleotides and  
15 any 3' overhang. In preferred embodiments asymmetrical modifications which result in one or more of the following are used: modifications of the 5' end of the sense strand which inhibit kinase activation of the sense strand, including, e.g., attachments of conjugates which target the molecule or the use modifications which protect against 5' exonucleolytic degradation; or modifications of either strand, but preferably the sense strand, which enhance  
20 binding between the sense and antisense strand and thereby promote a "tight" structure at this end of the molecule.

The end region of the iRNA agent defined by the 3' end of the sense strand and the 5' end of the antisense strand is also important for function. This region can include the terminal 2, 3, or 4 paired nucleotides and any 3' overhang. Preferred embodiments include  
25 asymmetrical modifications of either strand, but preferably the sense strand, which decrease binding between the sense and antisense strand and thereby promote an "open" structure at this end of the molecule. Such modifications include placing conjugates which target the molecule or modifications which promote nuclease resistance on the sense strand in this region. Modification of the antisense strand which inhibit kinase activation are avoided in  
30 preferred embodiments.

Exemplary modifications for asymmetrical placement in the sense strand include the following:

- (a) backbone modifications, e.g., modification of a backbone P, including replacement of P with S, or P substituted with alkyl or allyl, e.g., Me, and dithioates (S-P=S);  
5 these modifications can be used to promote nuclease resistance;
- (b) 2'-O alkyl, e.g., 2'-OMe, 3'-O alkyl, e.g., 3'-OMe (at terminal and/or internal positions); these modifications can be used to promote nuclease resistance or to enhance binding of the sense to the antisense strand, the 3' modifications can be used at the 5' end of the sense strand to avoid sense strand activation by RISC;
- 10 (c) 2'-5' linkages (with 2'-H, 2'-OH and 2'-OMe and with P=O or P=S) these modifications can be used to promote nuclease resistance or to inhibit binding of the sense to the antisense strand, or can be used at the 5' end of the sense strand to avoid sense strand activation by RISC;
- (d) L sugars (e.g., L ribose, L-arabinose with 2'-H, 2'-OH and 2'-OMe); these  
15 modifications can be used to promote nuclease resistance or to inhibit binding of the sense to the antisense strand, or can be used at the 5' end of the sense strand to avoid sense strand activation by RISC;
- (e) modified sugars (e.g., locked nucleic acids (LNA's), hexose nucleic acids (HNA's) and cyclohexene nucleic acids (CeNA's)); these modifications can be used to  
20 promote nuclease resistance or to inhibit binding of the sense to the antisense strand, or can be used at the 5' end of the sense strand to avoid sense strand activation by RISC;
- (f) nucleobase modifications (e.g., C-5 modified pyrimidines, N-2 modified purines, N-7 modified purines, N-6 modified purines), these modifications can be used to promote nuclease resistance or to enhance binding of the sense to the antisense strand;
- 25 (g) cationic groups and Zwitterionic groups (preferably at a terminus), these modifications can be used to promote nuclease resistance;
- (h) conjugate groups (preferably at terminal positions), e.g., naproxen, biotin, cholesterol, ibuprofen, folic acid, peptides, and carbohydrates; these modifications can be used to promote nuclease resistance or to target the molecule, or can be used at the 5' end of  
30 the sense strand to avoid sense strand activation by RISC.

Exemplary modifications for asymmetrical placement in the antisense strand include the following:

- (a) backbone modifications, e.g., modification of a backbone P, including replacement of P with S, or P substituted with alkyl or allyl, e.g., Me, and dithioates (S-P=S);
- 5 (b) 2'-O alkyl, e.g., 2'-OMe, (at terminal positions);
- (c) 2'-5' linkages (with 2'-H, 2'-OH and 2'-OMe) e.g., terminal at the 3' end); e.g., with P=O or P=S preferably at the 3'-end, these modifications are preferably excluded from the 5' end region as they may interfere with RISC enzyme activity such as kinase activity;
- 10 (d) L sugars (e.g., L ribose, L-arabinose with 2'-H, 2'-OH and 2'-OMe); e.g., terminal at the 3' end; e.g., with P=O or P=S preferably at the 3'-end, these modifications are preferably excluded from the 5' end region as they may interfere with kinase activity;
- (e) modified sugars (e.g., LNA's, HNA's and CeNA's); these modifications are preferably excluded from the 5' end region as they may contribute to unwanted enhancements of paring between the sense and antisense strands, it is often preferred to have
- 15 a "loose" structure in the 5' region, additionally, they may interfere with kinase activity;
- (f) nucleobase modifications (e.g., C-5 modified pyrimidines, N-2 modified purines, N-7 modified purines, N-6 modified purines);
- (g) cationic groups and Zwitterionic groups (preferably at a terminus);
- conjugate groups (preferably at terminal positions), e.g., naproxen, biotin, cholesterol,
- 20 ibuprofen, folic acid, peptides, and carbohydrates, but bulky groups or generally groups which inhibit RISC activity should be less preferred.

The 5'-OH of the antisense strand should be kept free to promote activity. In some preferred embodiments modifications that promote nuclease resistance should be included at the 3' end, particularly in the 3' overhang.

25 In another aspect, the invention features a method of optimizing, e.g., stabilizing, an iRNA agent. The method includes selecting a sequence having activity, introducing one or more asymmetric modifications into the sequence, wherein the introduction of the asymmetric modification optimizes a property of the iRNA agent but does not result in a decrease in activity.

30 The decrease in activity can be less than a preselected level of decrease. In preferred embodiments decrease in activity means a decrease of less than 5, 10, 20, 40, or

50 % activity, as compared with an otherwise similar iRNA lacking the introduced modification. Activity can, e.g., be measured in vivo, or in vitro, with a result in either being sufficient to demonstrate the required maintenance of activity.

The optimized property can be any property described herein and in particular the  
5 properties discussed in the section on asymmetrical modifications provided herein. The  
modification can be any asymmetrical modification, e.g., an asymmetric modification  
described in the section on asymmetrical modifications described herein. Particularly  
preferred asymmetric modifications are 2'-O alkyl modifications, e.g., 2'-OMe  
modifications, particularly in the sense sequence, and modifications of a backbone O,  
10 particularly phosphorothioate modifications, in the antisense sequence.

In a preferred embodiment a sense sequence is selected and provided with an  
asymmetrical modification, while in other embodiments an antisense sequence is selected  
and provided with an asymmetrical modification. In some embodiments both sense and  
antisense sequences are selected and each provided with one or more asymmetrical  
15 modifications.

Multiple asymmetric modifications can be introduced into either or both of the sense  
and antisense sequence. A sequence can have at least 2, 4, 6, 8, or more modifications and  
all or substantially all of the monomers of a sequence can be modified.

Table: 2. Some examples of Asymmetric Modification

This table shows examples having strand I with a selected modification and strand II  
 5 with a selected modification.

Strand I	Strand II
Nuclease Resistance (e.g. 2'-OMe)	Biodistribution (e.g., P=S)
Biodistribution conjugate (e.g. Lipophile)	Protein Binding Functionality (e.g. Naproxen)
Tissue Distribution Functionality (e.g. Carbohydrates)	Cell Targeting Functionality (e.g. Folate for cancer cells)
Tissue Distribution Functionality (e.g. Liver Cell Targeting Carbohydrates)	Fusogenic Functionality (e.g. Polyethylene imines)
Cancer Cell Targeting (e. g. RGD peptides and imines)	Fusogenic Functionality (e.g. peptides)
Nuclease Resistance (e.g. 2'-OMe)	Increase in binding Affinity (5-Me-C, 5-Me-U, 2- thio-U, 2-amino-A, G-clamp, LNA)
Tissue Distribution Functionality	RISC activity improving Functionality
Helical conformation changing Functionalities	Tissue Distribution Functionality (P=S; lipophile, carbohydrates)



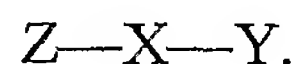
### Z-X-Y Architecture

In one aspect, the invention features an iRNA agent which can have a Z-X-Y  
5 architecture or structure such as those described herein and those described in copending, co-  
owned United States Provisional Application Serial No. 60/510,246 (Attorney Docket No.  
14174-079P02), filed on October 9, 2003, which is hereby incorporated by reference, and in  
copending, co-owned United States Provisional Application Serial No. 60/510,318 (Attorney  
Docket No. 14174-079P03), filed on October 10, 2003, which is hereby incorporated by  
10 reference.

In addition, the invention includes iRNA agents having a Z-X-Y structure and another  
element described herein. E.g., the invention includes an iRNA agent described herein, e.g.,  
a palindromic iRNA agent, an iRNA agent having a non canonical pairing, an iRNA agent  
which targets a gene described herein, e.g., a gene active in the liver, an iRNA associated  
15 with an amphipathic delivery agent described herein, an iRNA associated with a drug  
delivery module described herein, an iRNA agent administered as described herein, or an  
iRNA agent formulated as described herein, which also incorporates a Z-X-Y architecture.

The invention provides an iRNA agent having a first segment, the Z region, a second  
segment, the X region, and optionally a third region, the Y region:

20



It may be desirable to modify subunits in one or both of Z and/or Y on one hand and X  
on the other hand. In some cases they will have the same modification or the same class of  
25 modification but it will more often be the case that the modifications made in Z and/or Y will  
differ from those made in X.

The Z region typically includes a terminus of an iRNA agent. The length of the Z  
region can vary, but will typically be from 2-14, more preferably 2-10, subunits in length. It  
typically is single stranded, i.e., it will not base pair with bases of another strand, though it  
30 may in some embodiments self associate, e.g., to form a loop structure. Such structures can  
be formed by the end of a strand looping back and forming an intrastrand duplex. E.g., 2, 3,

4, 5 or more intra-strand bases pairs can form, having a looped out or connecting region, typically of 2 or more subunits which do not pair. This can occur at one or both ends of a strand. A typical embodiment of a Z region is a single strand overhang, e.g., an over hang of the length described elsewhere herein. The Z region can thus be or include a 3' or 5' terminal single strand. It can be sense or antisense strand but if it is antisense it is preferred that it is a 3'-overhang. Typical inter-subunit bonds in the Z region include: P=O; P=S; S-P=S; P-NR<sub>2</sub>; and P-BR<sub>2</sub>. Chiral P=X, where X is S, N, or B) inter-subunit bonds can also be present. (These inter-subunit bonds are discussed in more detail elsewhere herein.) Other preferred Z region subunit modifications (also discussed elsewhere herein) can include: 3'-OR, 3'SR, 2'-OMe, 3'-OMe, and 2'OH modifications and moieties; alpha configuration bases; and 2' arabino modifications.

The X region will in most cases be duplexed, in the case of a single strand iRNA agent, with a corresponding region of the single strand, or in the case of a double stranded iRNA agent, with the corresponding region of the other strand. The length of the X region can vary but will typically be between 10-45 and more preferably between 15 and 35 subunits. Particularly preferred region X's will include 17, 18, 19, 29, 21, 22, 23, 24, or 25 nucleotide pairs, though other suitable lengths are described elsewhere herein and can be used. Typical X region subunits include 2'-OH subunits. In typical embodiments phosphate inter-subunit bonds are preferred while phosphorothioate or non-phosphate bonds are absent. Other modifications preferred in the X region include: modifications to improve binding, e.g., nucleobase modifications; cationic nucleobase modifications; and C-5 modified pyrimidines, e.g., allylamines. Some embodiments have 4 or more consecutive 2'OH subunits. While the use of phosphorothioate is sometimes non preferred they can be used if they connect less than 4 consecutive 2'OH subunits.

The Y region will generally conform to the the parameters set out for the Z regions. However, the X and Z regions need not be the same, different types and numbers of modifications can be present, and infact, one will usually be a 3' overhang and one will usually be a 5' overhang.

In a preferred embodiment the iRNA agent will have a Y and/or Z region each having ribonucleosides in which the 2'-OH is substituted, e.g., with 2'-OMe or other alkyl; and an X

region that includes at least four consecutive ribonucleoside subunits in which the 2'-OH remains unsubstituted.

The subunit linkages (the linkages between subunits) of an iRNA agent can be modified, e.g., to promote resistance to degradation. Numerous examples of such  
5 modifications are disclosed herein, one example of which is the phosphorothioate linkage. These modifications can be provided between the subunits of any of the regions, Y, X, and Z. However, it is preferred that their occurrence is minimized and in particular it is preferred that consecutive modified linkages be avoided.

In a preferred embodiment the iRNA agent will have a Y and Z region each having  
10 ribonucleosides in which the 2'-OH is substituted, e.g., with 2'-OMe; and an X region that includes at least four consecutive subunits, e.g., ribonucleoside subunits in which the 2'-OH remains unsubstituted.

As mentioned above, the subunit linkages of an iRNA agent can be modified, e.g., to promote resistance to degradation. These modifications can be provided between the  
15 subunits of any of the regions, Y, X, and Z. However, it is preferred that they are minimized and in particular it is preferred that consecutive modified linkages be avoided.

Thus, in a preferred embodiment, not all of the subunit linkages of the iRNA agent are modified and more preferably the maximum number of consecutive subunits linked by other than a phosphodiester bond will be 2, 3, or 4. Particularly preferred iRNA agents will not  
20 have four or more consecutive subunits, e.g., 2'-hydroxyl ribonucleoside subunits, in which each subunit is joined by modified linkages – i.e. linkages that have been modified to stabilize them from degradation as compared to the phosphodiester linkages that naturally occur in RNA and DNA.

It is particularly preferred to minimize the occurrence in region X. Thus, in preferred  
25 embodiments each of the nucleoside subunit linkages in X will be phosphodiester linkages, or if subunit linkages in region X are modified, such modifications will be minimized. E.g., although the Y and/or Z regions can include inter subunit linkages which have been stabilized against degradation, such modifications will be minimized in the X region, and in particular consecutive modifications will be minimized. Thus, in preferred embodiments the  
30 maximum number of consecutive subunits linked by other than a phosphodiester bond will be 2, 3, or 4. Particularly preferred X regions will not have four or more consecutive subunits,

e.g., 2'-hydroxyl ribonucleoside subunits, in which each subunits is joined by modified linkages – i.e. linkages that have been modified to stabilize them from degradation as compared to the phosphodiester linkages that naturally occur in RNA and DNA.

In a preferred embodiment Y and /or Z will be free of phosphorothioate linkages, though either or both may contain other modifications, e.g., other modifications of the subunit linkages.

In a preferred embodiment region X, or in some cases, the entire iRNA agent, has no more than 3 or no more than 4 subunits having identical 2' moieties.

In a preferred embodiment region X, or in some cases, the entire iRNA agent, has no more than 3 or no more than 4 subunits having identical subunit linkages.

In a preferred embodiment one or more phosphorothioate linkages (or other modifications of the subunit linkage) are present in Y and/or Z, but such modified linkages do not connect two adjacent subunits, e.g., nucleosides, having a 2' modification, e.g., a 2'-O-alkyl moiety. E.g., any adjacent 2'-O-alkyl moieties in the Y and/or Z, are connected by a linkage other than a a phosphorothioate linkage.

In a preferred embodiment each of Y and/or Z independently has only one phosphorothioate linkage between adjacent subunits, e.g., nucleosides, having a 2' modification, e.g., 2'-O-alkyl nucleosides. If there is a second set of adjacent subunits, e.g., nucleosides, having a 2' modification, e.g., 2'-O-alkyl nucleosides, in Y and/or Z that second set is connected by a linkage other than a phosphorothioate linkage, e.g., a modified linkage other than a phosphorothioate linkage.

In a preferred embodiment each of Y and/or Z independently has more than one phosphorothioate linkage connecting adjacent pairs of subunits, e.g., nucleosides, having a 2' modification, e.g., 2'-O-alkyl nucleosides, but at least one pair of adjacent subunits, e.g., nucleosides, having a 2' modification, e.g., 2'-O-alkyl nucleosides, are be connected by a linkage other than a phosphorothioate linkage, e.g., a modified linkage other than a phosphorothioate linkage.

In a preferred embodiment one of the above recited limitation on adjacent subunits in Y and or Z is combined with a limitation on the subunits in X. E.g., one or more phosphorothioate linkages (or other modifications of the subunit linkage) are present in Y and/or Z, but such modified linkages do not connect two adjacent subunits, e.g., nucleosides,

having a 2' modification, e.g., a 2'-O-alkyl moiety. E.g., any adjacent 2'-O-alkyl moieties in the Y and/or Z, are connected by a linkage other than a phosphorothioate linkage. In addition, the X region has no more than 3 or no more than 4 identical subunits, e.g., subunits having identical 2' moieties or the X region has no more than 3 or no more than 4 subunits having identical subunit linkages.

A Y and/or Z region can include at least one, and preferably 2, 3 or 4 of a modification disclosed herein. Such modifications can be chosen, independently, from any modification described herein, e.g., from nuclease resistant subunits, subunits with modified bases, subunits with modified intersubunit linkages, subunits with modified sugars, and subunits linked to another moiety, e.g., a targeting moiety. In a preferred embodiment more than 1 of such subunits can be present but in some embodiments it is preferred that no more than 1, 2, 3, or 4 of such modifications occur, or occur consecutively. In a preferred embodiment the frequency of the modification will differ between Y and/or Z and X, e.g., the modification will be present one of Y and/or Z or X and absent in the other.

An X region can include at least one, and preferably 2, 3 or 4 of a modification disclosed herein. Such modifications can be chosen, independently, from any modification described herein, e.g., from nuclease resistant subunits, subunits with modified bases, subunits with modified intersubunit linkages, subunits with modified sugars, and subunits linked to another moiety, e.g., a targeting moiety. In a preferred embodiment more than 1 of such subunits can be present but in some embodiments it is preferred that no more than 1, 2, 3, or 4 of such modifications occur, or occur consecutively.

An RRMS (described elsewhere herein) can be introduced at one or more points in one or both strands of a double-stranded siRNA agent. An RRMS can be placed in a Y and/or Z region, at or near (within 1, 2, or 3 positions) of the 3' or 5' end of the sense strand or at near (within 2 or 3 positions of) the 3' end of the antisense strand. In some embodiments it is preferred to not have an RRMS at or near (within 1, 2, or 3 positions of) the 5' end of the antisense strand. An RRMS can be positioned in the X region, and will preferably be positioned in the sense strand or in an area of the antisense strand not critical for antisense binding to the target.

30



### Differential Modification of Terminal Duplex Stability

In one aspect, the invention features an iRNA agent which can have differential modification of terminal duplex stability (DMTDS).

5 In addition, the invention includes iRNA agents having DMTDS and another element described herein. E.g., the invention includes an iRNA agent described herein, e.g., a palindromic iRNA agent, an iRNA agent having a non canonical pairing, an iRNA agent which targets a gene described herein, e.g., a gene active in the liver, an iRNA agent having an architecture or structure described herein, an iRNA associated with an amphipathic  
10 delivery agent described herein, an iRNA associated with a drug delivery module described herein, an iRNA agent administered as described herein, or an iRNA agent formulated as described herein, which also incorporates DMTDS.

iRNA agents can be optimized by increasing the propensity of the duplex to disassociate or melt (decreasing the free energy of duplex association), in the region of the 5'  
15 end of the antisense strand duplex. This can be accomplished, e.g., by the inclusion of subunits which increase the propensity of the duplex to disassociate or melt in the region of the 5' end of the antisense strand. It can also be accomplished by the attachment of a ligand that increases the propensity of the duplex to disassociate or melt in the region of the 5' end. While not wishing to be bound by theory, the effect may be due to promoting the effect of an  
20 enzyme such as helicase, for example, promoting the effect of the enzyme in the proximity of the 5' end of the antisense strand.

The inventors have also discovered that iRNA agents can be optimized by decreasing the propensity of the duplex to disassociate or melt (increasing the free energy of duplex association), in the region of the 3' end of the antisense strand duplex. This can be  
25 accomplished, e.g., by the inclusion of subunits which decrease the propensity of the duplex to disassociate or melt in the region of the 3' end of the antisense strand. It can also be accomplished by the attachment of ligand that decreases the propensity of the duplex to disassociate or melt in the region of the 5' end.

Modifications which increase the tendency of the 5' end of the duplex to dissociate  
30 can be used alone or in combination with other modifications described herein, e.g., with modifications which decrease the tendency of the 3' end of the duplex to dissociate.

Likewise, modifications which decrease the tendency of the 3' end of the duplex to dissociate can be used alone or in combination with other modifications described herein, e.g., with modifications which increase the tendency of the 5' end of the duplex to dissociate.

*Decreasing the stability of the AS 5' end of the duplex*

5 Subunit pairs can be ranked on the basis of their propensity to promote dissociation or melting (e.g., on the free energy of association or dissociation of a particular pairing, the simplest approach is to examine the pairs on an individual pair basis, though next neighbor or similar analysis can also be used). In terms of promoting dissociation:

10 A:U is preferred over G:C;  
 G:U is preferred over G:C;  
 I:C is preferred over G:C (I=inosine);  
 mismatches, e.g., non-canonical or other than canonical pairings (as described elsewhere herein) are preferred over canonical (A:T, A:U, G:C) pairings;  
 15 pairings which include a universal base are preferred over canonical pairings.

A typical ds iRNA agent can be diagrammed as follows:

20 S 5' R<sub>1</sub> N<sub>1</sub> N<sub>2</sub> N<sub>3</sub> N<sub>4</sub> N<sub>5</sub> [N] N<sub>-5</sub> N<sub>-4</sub> N<sub>-3</sub> N<sub>-2</sub> N<sub>-1</sub> R<sub>2</sub> 3'  
 AS 3' R<sub>3</sub> N<sub>1</sub> N<sub>2</sub> N<sub>3</sub> N<sub>4</sub> N<sub>5</sub> [N] N<sub>-5</sub> N<sub>-4</sub> N<sub>-3</sub> N<sub>-2</sub> N<sub>-1</sub> R<sub>4</sub> 5'  
 S:AS P<sub>1</sub> P<sub>2</sub> P<sub>3</sub> P<sub>4</sub> P<sub>5</sub> [N] P<sub>-5</sub> P<sub>-4</sub> P<sub>-3</sub> P<sub>-2</sub> P<sub>-1</sub> 5'

25 S indicates the sense strand; AS indicates antisense strand; R<sub>1</sub> indicates an optional (and nonpreferred) 5' sense strand overhang; R<sub>2</sub> indicates an optional (though preferred) 3' sense overhang; R<sub>3</sub> indicates an optional (though preferred) 3' antisense sense overhang; R<sub>4</sub> indicates an optional (and nonpreferred) 5' antisense overhang; N indicates subunits; [N] indicates that additional subunit pairs may be present; and P<sub>x</sub>, indicates a paring of sense N<sub>x</sub> and antisense N<sub>x</sub>. Overhangs are not shown in the P diagram. In some embodiments a 3' AS  
 30 overhang corresponds to region Z, the duplex region corresponds to region X, and the 3' S strand overhang corresponds to region Y, as described elsewhere herein. (The diagram is not

meant to imply maximum or minimum lengths, on which guidance is provided elsewhere herein.)

It is preferred that pairings which decrease the propensity to form a duplex are used at 1 or more of the positions in the duplex at the 5' end of the AS strand. The terminal pair (the most 5' pair in terms of the AS strand) is designated as P<sub>-1</sub>, and the subsequent pairing positions (going in the 3' direction in terms of the AS strand) in the duplex are designated, P<sub>-2</sub>, P<sub>-3</sub>, P<sub>-4</sub>, P<sub>-5</sub>, and so on. The preferred region in which to modify to modulate duplex formation is at P<sub>-5</sub> through P<sub>-1</sub>, more preferably P<sub>-4</sub> through P<sub>-1</sub>, more preferably P<sub>-3</sub> through P<sub>-1</sub>. Modification at P<sub>-1</sub>, is particularly preferred, alone or with modification(s) other position(s), e.g., any of the positions just identified. It is preferred that at least 1, and more preferably 2, 3, 4, or 5 of the pairs of one of the recited regions be chosen independently from the group of:

A:U  
G:U  
I:C

mismatched pairs, e.g., non-canonical or other than canonical pairings or pairings which include a universal base.

In preferred embodiments the change in subunit needed to achieve a pairing which promotes dissociation will be made in the sense strand, though in some embodiments the change will be made in the antisense strand.

In a preferred embodiment the at least 2, or 3, of the pairs in P<sub>-1</sub>, through P<sub>-4</sub>, are pairs which promote dissociation.

In a preferred embodiment the at least 2, or 3, of the pairs in P<sub>-1</sub>, through P<sub>-4</sub>, are A:U.

In a preferred embodiment the at least 2, or 3, of the pairs in P<sub>-1</sub>, through P<sub>-4</sub>, are G:U.

In a preferred embodiment the at least 2, or 3, of the pairs in P<sub>-1</sub>, through P<sub>-4</sub>, are I:C.

In a preferred embodiment the at least 2, or 3, of the pairs in P<sub>-1</sub>, through P<sub>-4</sub>, are mismatched pairs, e.g., non-canonical or other than canonical pairings pairings.

In a preferred embodiment the at least 2, or 3, of the pairs in P<sub>-1</sub>, through P<sub>-4</sub>, are pairings which include a universal base.

*Increasing the stability of the AS 3' end of the duplex*

Subunit pairs can be ranked on the basis of their propensity to promote stability and inhibit dissociation or melting (e.g., on the free energy of association or dissociation of a particular pairing, the simplest approach is to examine the pairs on an individual pair basis, though next neighbor or similar analysis can also be used). In terms of promoting duplex stability:

G:C is preferred over A:U

Watson-Crick matches (A:T, A:U, G:C) are preferred over non-canonical or other than canonical pairings

analogs that increase stability are preferred over Watson-Crick matches (A:T, A:U, G:C)

2-amino-A:U is preferred over A:U

2-thio U or 5 Me-thio-U:A are preferred over U:A

G-clamp (an analog of C having 4 hydrogen bonds):G is preferred over C:G

guanadinium-G-clamp:G is preferred over C:G

psuedo uridine:A is preferred over U:A

sugar modifications, e.g., 2' modifications, e.g., 2'F, ENA, or LNA, which enhance binding are preferred over non-modified moieties and can be present on one or both strands to enhance stability of the duplex. It is preferred that pairings which increase the propensity to form a duplex are used at 1 or more of the positions in the duplex at the 3' end of the AS strand. The terminal pair (the most 3' pair in terms of the AS strand) is designated as P<sub>1</sub>, and the subsequent pairing positions (going in the 5' direction in terms of the AS strand) in the duplex are designated, P<sub>2</sub>, P<sub>3</sub>, P<sub>4</sub>, P<sub>5</sub>, and so on. The preferred region in which to modify to modulate duplex formation is at P<sub>5</sub> through P<sub>1</sub>, more preferably P<sub>4</sub> through P<sub>1</sub>, more preferably P<sub>3</sub> through P<sub>1</sub>. Modification at P<sub>1</sub>, is particularly preferred, alone or with modification(s) at other position(s), e.g., any of the positions just identified. It is preferred that at least 1, and more preferably 2, 3, 4, or 5 of the pairs of the recited regions be chosen independently from the group of:

G:C

a pair having an analog that increases stability over Watson-Crick matches (A:T, A:U, G:C)

2-amino-A:U

2-thio U or 5 Me-thio-U:A

5 G-clamp (an analog of C having 4 hydrogen bonds):G  
guanadinium-G-clamp:G  
psuedo uridine:A

a pair in which one or both subunits has a sugar modification, e.g., a 2' modification, e.g., 2'F, ENA, or LNA, which enhance binding.

10

In a preferred embodiment the at least 2, or 3, of the pairs in P<sub>1</sub>, through P<sub>4</sub>, are pairs which promote duplex stability.

In a preferred embodiment the at least 2, or 3, of the pairs in P<sub>1</sub>, through P<sub>4</sub>, are G:C.

15 In a preferred embodiment the at least 2, or 3, of the pairs in P<sub>1</sub>, through P<sub>4</sub>, are a pair having an analog that increases stability over Watson-Crick matches.

In a preferred embodiment the at least 2, or 3, of the pairs in P<sub>1</sub>, through P<sub>4</sub>, are 2-amino-A:U.

In a preferred embodiment the at least 2, or 3, of the pairs in P<sub>1</sub>, through P<sub>4</sub>, are 2-thio U or 5 Me-thio-U:A.

20 In a preferred embodiment the at least 2, or 3, of the pairs in P<sub>1</sub>, through P<sub>4</sub>, are G-clamp:G.

In a preferred embodiment the at least 2, or 3, of the pairs in P<sub>1</sub>, through P<sub>4</sub>, are guanidinium-G-clamp:G.

25 In a preferred embodiment the at least 2, or 3, of the pairs in P<sub>1</sub>, through P<sub>4</sub>, are psuedo uridine:A.

In a preferred embodiment the at least 2, or 3, of the pairs in P<sub>1</sub>, through P<sub>4</sub>, are a pair in which one or both subunits has a sugar modification, e.g., a 2' modification, e.g., 2'F, ENA, or LNA, which enhances binding.

G-clamps and guanidinium G-clamps are discussed in the following references:

30 Holmes and Gait, "The Synthesis of 2'-O-Methyl G-Clamp Containing Oligonucleotides and Their Inhibition of the HIV-1 Tat-TAR Interaction," Nucleosides, Nucleotides & Nucleic



Acids, 22:1259-1262, 2003; Holmes *et al.*, "Steric inhibition of human immunodeficiency virus type-1 Tat-dependent trans-activation in vitro and in cells by oligonucleotides containing 2'-O-methyl G-clamp ribonucleoside analogues," Nucleic Acids Research, 31:2759-2768, 2003; Wilds, *et al.*, "Structural basis for recognition of guanosine by a synthetic tricyclic cytosine analogue: Guanidinium G-clamp," Helvetica Chimica Acta, 86:966-978, 2003; Rajeev, *et al.*, "High-Affinity Peptide Nucleic Acid Oligomers Containing Tricyclic Cytosine Analogues," Organic Letters, 4:4395-4398, 2002; Ausin, *et al.*, "Synthesis of Amino- and Guanidino-G-Clamp PNA Monomers," Organic Letters, 4:4073-4075, 2002; Maier *et al.*, "Nuclease resistance of oligonucleotides containing the tricyclic cytosine analogues phenoxazine and 9-(2-aminoethoxy)-phenoxazine ("G-clamp") and origins of their nuclease resistance properties," Biochemistry, 41:1323-7, 2002; Flanagan, *et al.*, "A cytosine analog that confers enhanced potency to antisense oligonucleotides," Proceedings Of The National Academy Of Sciences Of The United States Of America, 96:3513-8, 1999.

Simultaneously decreasing the stability of the AS 5' end of the duplex and increasing the stability of the AS 3' end of the duplex

As is discussed above, an iRNA agent can be modified to both decrease the stability of the AS 5' end of the duplex and increase the stability of the AS 3' end of the duplex. This can be effected by combining one or more of the stability decreasing modifications in the AS 5' end of the duplex with one or more of the stability increasing modifications in the AS 3' end of the duplex. Accordingly a preferred embodiment includes modification in P<sub>-5</sub> through P<sub>-1</sub>, more preferably P<sub>-4</sub> through P<sub>-1</sub> and more preferably P<sub>-3</sub> through P<sub>-1</sub>. Modification at P<sub>-1</sub>, is particularly preferred, alone or with other position, e.g., the positions just identified. It is preferred that at least 1, and more preferably 2, 3, 4, or 5 of the pairs of one of the recited regions of the AS 5' end of the duplex region be chosen independently from the group of:

A:U

G:U

I:C

mismatched pairs, e.g., non-canonical or other than canonical pairings which include a universal base; and

a modification in P<sub>5</sub> through P<sub>1</sub>, more preferably P<sub>4</sub> through P<sub>1</sub> and more preferably P<sub>3</sub> through P<sub>1</sub>. Modification at P<sub>1</sub>, is particularly preferred, alone or with other position, e.g., the positions just identified. It is preferred that at least 1, and more preferably 2, 3, 4, or 5 of the pairs of one of the recited regions of the AS 3' end of the duplex region be chosen independently from the group of:

10 G:C

a pair having an analog that increases stability over Watson-Crick matches (A:T, A:U, G:C)

2-amino-A:U

2-thio U or 5 Me-thio-U:A

15 G-clamp (an analog of C having 4 hydrogen bonds):G

guanadinium-G-clamp:G

psuedo uridine:A

a pair in which one or both subunits has a sugar modification, e.g., a 2' modification, e.g., 2'F, ENA, or LNA, which enhance binding.

20

The invention also includes methods of selecting and making iRNA agents having DMTDS. E.g., when screening a target sequence for candidate sequences for use as iRNA agents one can select sequences having a DMTDS property described herein or one which can be modified, preferably with as few changes as possible, especially to the

25 AS strand, to provide a desired level of DMTDS.

The invention also includes, providing a candidate iRNA agent sequence, and modifying at least one P in P<sub>5</sub> through P<sub>1</sub> and/or at least one P in P<sub>5</sub> through P<sub>1</sub> to provide a DMTDS iRNA agent.

DMTDS iRNA agents can be used in any method described herein, e.g., to silence  
30 any gene disclosed herein, to treat any disorder described herein, in any formulation described herein, and generally in and/or with the methods and compositions described

elsewhere herein. DMTDS iRNA agents can incorporate other modifications described herein, e.g., the attachment of targeting agents or the inclusion of modifications which enhance stability, e.g., the inclusion of nuclease resistant monomers or the inclusion of single strand overhangs (e.g., 3' AS overhangs and/or 3' S strand overhangs) which self associate to  
5 form intrastrand duplex structure.

Preferably these iRNA agents will have an architecture described herein.

### **Other Embodiments**

#### **In vivo Delivery**

10 An iRNA agent can be linked, e.g., noncovalently linked to a polymer for the efficient delivery of the iRNA agent to a subject, e.g., a mammal, such as a human. The iRNA agent can, for example, be complexed with cyclodextrin. Cyclodextrins have been used as delivery vehicles of therapeutic compounds. Cyclodextrins can form inclusion complexes with drugs that are able to fit into the hydrophobic cavity of the cyclodextrin. In other examples,  
15 cyclodextrins form non-covalent associations with other biologically active molecules such as oligonucleotides and derivatives thereof. The use of cyclodextrins creates a water-soluble drug delivery complex, that can be modified with targeting or other functional groups. Cyclodextrin cellular delivery system for oligonucleotides described in U.S. Pat. No. 5,691,316, which is hereby incorporated by reference, are suitable for use in methods of the  
20 invention. In this system, an oligonucleotide is noncovalently complexed with a cyclodextrin, or the oligonucleotide is covalently bound to adamantine which in turn is non-covalently associated with a cyclodextrin.

The delivery molecule can include a linear cyclodextrin copolymer or a linear oxidized cyclodextrin copolymer having at least one ligand bound to the cyclodextrin  
25 copolymer. Delivery systems, as described in U.S. Patent No. 6,509,323, herein incorporated by reference, are suitable for use in methods of the invention. An iRNA agent can be bound to the linear cyclodextrin copolymer and/or a linear oxidized cyclodextrin copolymer. Either or both of the cyclodextrin or oxidized cyclodextrin copolymers can be crosslinked to another polymer and/or bound to a ligand.

30 A composition for iRNA delivery can employ an "inclusion complex," a molecular compound having the characteristic structure of an adduct. In this structure, the "host

molecule" spatially encloses at least part of another compound in the delivery vehicle. The enclosed compound (the "guest molecule") is situated in the cavity of the host molecule without affecting the framework structure of the host. A "host" is preferably cyclodextrin, but can be any of the molecules suggested in U.S. Patent Publ. 2003/0008818, herein  
5 incorporated by reference.

Cyclodextrins can interact with a variety of ionic and molecular species, and the resulting inclusion compounds belong to the class of "host-guest" complexes. Within the host-guest relationship, the binding sites of the host and guest molecules should be complementary in the stereoelectronic sense. A composition of the invention can contain at  
10 least one polymer and at least one therapeutic agent, generally in the form of a particulate composite of the polymer and therapeutic agent, *e.g.*, the iRNA agent. The iRNA agent can contain one or more complexing agents. At least one polymer of the particulate composite can interact with the complexing agent in a host-guest or a guest-host interaction to form an inclusion complex between the polymer and the complexing agent. The polymer and, more  
15 particularly, the complexing agent can be used to introduce functionality into the composition. For example, at least one polymer of the particulate composite has host functionality and forms an inclusion complex with a complexing agent having guest functionality. Alternatively, at least one polymer of the particulate composite has guest functionality and forms an inclusion complex with a complexing agent having host  
20 functionality. A polymer of the particulate composite can also contain both host and guest functionalities and form inclusion complexes with guest complexing agents and host complexing agents. A polymer with functionality can, for example, facilitate cell targeting and/or cell contact (*e.g.*, targeting or contact to a liver cell), intercellular trafficking, and/or cell entry and release.

25 Upon forming the particulate composite, the iRNA agent may or may not retain its biological or therapeutic activity. Upon release from the therapeutic composition, specifically, from the polymer of the particulate composite, the activity of the iRNA agent is restored. Accordingly, the particulate composite advantageously affords the iRNA agent protection against loss of activity due to, for example, degradation and offers enhanced  
30 bioavailability. Thus, a composition may be used to provide stability, particularly storage or solution stability, to an iRNA agent or any active chemical compound. The iRNA agent may

be further modified with a ligand prior to or after particulate composite or therapeutic composition formation. The ligand can provide further functionality. For example, the ligand can be a targeting moiety.

5           Physiological Effects

The iRNA agents described herein can be designed such that determining therapeutic toxicity is made easier by the complementarity of the iRNA agent with both a human and a non-human animal sequence. By these methods, an iRNA agent can consist of a sequence that is fully complementary to a nucleic acid sequence from a human and a nucleic acid  
10 sequence from at least one non-human animal, *e.g.*, a non-human mammal, such as a rodent, ruminant or primate. For example, the non-human mammal can be a mouse, rat, dog, pig, goat, sheep, cow, monkey, *Pan paniscus*, *Pan troglodytes*, *Macaca mulatto*, or *Cynomolgus* monkey. The sequence of the iRNA agent could be complementary to sequences within homologous genes, *e.g.*, oncogenes or tumor suppressor genes, of the non-human mammal  
15 and the human. By determining the toxicity of the iRNA agent in the non-human mammal, one can extrapolate the toxicity of the iRNA agent in a human. For a more strenuous toxicity test, the iRNA agent can be complementary to a human and more than one, *e.g.*, two or three or more, non-human animals.

The methods described herein can be used to correlate any physiological effect of an iRNA  
20 agent on a human, *e.g.*, any unwanted effect, such as a toxic effect, or any positive, or desired effect.

Delivery Module

In one aspect, the invention features a drug delivery conjugate or module, such as  
25 those described herein and those described in copending, co-owned United States Provisional Application Serial No. 60/454,265, filed on March 12, 2003, which is hereby incorporated by reference.

In addition, the invention includes iRNA agents described herein, *e.g.*, a palindromic iRNA agent, an iRNA agent having a non canonical pairing, an iRNA agent which targets a  
30 gene described herein, *e.g.*, a gene active in the liver, an iRNA agent having a chemical modification described herein, *e.g.*, a modification which enhances resistance to degradation,



an iRNA agent having an architecture or structure described herein, an iRNA agent administered as described herein, or an iRNA agent formulated as described herein, combined with, associated with, and delivered by such a drug delivery conjugate or module.

The iRNA agents can be complexed to a delivery agent that features a modular complex. The complex can include a carrier agent linked to one or more of (preferably two or more, more preferably all three of): (a) a condensing agent (*e.g.*, an agent capable of attracting, *e.g.*, binding, a nucleic acid, *e.g.*, through ionic or electrostatic interactions); (b) a fusogenic agent (*e.g.*, an agent capable of fusing and/or being transported through a cell membrane, *e.g.*, an endosome membrane); and (c) a targeting group, *e.g.*, a cell or tissue targeting agent, *e.g.*, a lectin, glycoprotein, lipid or protein, *e.g.*, an antibody, that binds to a specified cell type such as a cancer cell, endothelial cell or bone cell.

An iRNA agent, *e.g.*, iRNA agent or sRNA agent described herein, can be linked, *e.g.*, coupled or bound, to the modular complex. The iRNA agent can interact with the condensing agent of the complex, and the complex can be used to deliver an iRNA agent to a cell, *e.g.*, *in vitro* or *in vivo*. For example, the complex can be used to deliver an iRNA agent to a subject in need thereof, *e.g.*, to deliver an iRNA agent to a subject having a disorder, *e.g.*, a disorder described herein, such as a disease or disorder of the liver.

The fusogenic agent and the condensing agent can be different agents or the one and the same agent. For example, a polyamino chain, *e.g.*, polyethyleneimine (PEI), can be the fusogenic and/or the condensing agent.

The delivery agent can be a modular complex. For example, the complex can include a carrier agent linked to one or more of (preferably two or more, more preferably all three of):

(a) a condensing agent (*e.g.*, an agent capable of attracting, *e.g.*, binding, a nucleic acid, *e.g.*, through ionic interaction),

(b) a fusogenic agent (*e.g.*, an agent capable of fusing and/or being transported through a cell membrane, *e.g.*, an endosome membrane), and

(c) a targeting group, *e.g.*, a cell or tissue targeting agent, *e.g.*, a lectin, glycoprotein, lipid or protein, *e.g.*, an antibody, that binds to a specified cell type such as a cancer cell, endothelial cell, bone cell. A targeting group can be a thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, Mucin carbohydrate, multivalent lactose, multivalent

galactose, N-acetyl-galactosamine, N-acetyl-gulucosamine multivalent mannose, multivalent fucose, glycosylated polyaminoacids, multivalent galactose, transferrin, bisphosphonate, polyglutamate, polyaspartate, a lipid, cholesterol, a steroid, bile acid, folate, vitamin B12, biotin, Neproxin, or an RGD peptide or RGD peptide mimetic.

5

### *Carrier agents*

The carrier agent of a modular complex described herein can be a substrate for attachment of one or more of: a condensing agent, a fusogenic agent, and a targeting group. The carrier agent would preferably lack an endogenous enzymatic activity. The agent would preferably be a biological molecule, preferably a macromolecule. Polymeric biological carriers are preferred. It would also be preferred that the carrier molecule be biodegradable..

The carrier agent can be a naturally occurring substance, such as a protein (*e.g.*, human serum albumin (HSA), low-density lipoprotein (LDL), or globulin); carbohydrate (*e.g.*, a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin or hyaluronic acid); or lipid. The carrier molecule can also be a recombinant or synthetic molecule, such as a synthetic polymer, *e.g.*, a synthetic polyamino acid. Examples of polyamino acids include polylysine (PLL), poly L-aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolide) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacrylic acid), N-isopropylacrylamide polymers, or polyphosphazine. Other useful carrier molecules can be identified by routine methods.

A carrier agent can be characterized by one or more of: (a) is at least 1 Da in size; (b) has at least 5 charged groups, preferably between 5 and 5000 charged groups; (c) is present in the complex at a ratio of at least 1:1 carrier agent to fusogenic agent; (d) is present in the complex at a ratio of at least 1:1 carrier agent to condensing agent; (e) is present in the complex at a ratio of at least 1:1 carrier agent to targeting agent.

### *Fusogenic agents*

A fusogenic agent of a modular complex described herein can be an agent that is responsive to, *e.g.*, changes charge depending on, the pH environment. Upon encountering the pH of an endosome, it can cause a physical change, *e.g.*, a change in osmotic properties

which disrupts or increases the permeability of the endosome membrane. Preferably, the fusogenic agent changes charge, *e.g.*, becomes protonated, at pH lower than physiological range. For example, the fusogenic agent can become protonated at pH 4.5-6.5. The fusogenic agent can serve to release the iRNA agent into the cytoplasm of a cell after the  
5 complex is taken up, *e.g.*, via endocytosis, by the cell, thereby increasing the cellular concentration of the iRNA agent in the cell.

In one embodiment, the fusogenic agent can have a moiety, *e.g.*, an amino group, which, when exposed to a specified pH range, will undergo a change, *e.g.*, in charge, *e.g.*, protonation. The change in charge of the fusogenic agent can trigger a change, *e.g.*, an  
10 osmotic change, in a vesicle, *e.g.*, an endocytic vesicle, *e.g.*, an endosome. For example, the fusogenic agent, upon being exposed to the pH environment of an endosome, will cause a solubility or osmotic change substantial enough to increase the porosity of (preferably, to rupture) the endosomal membrane.

The fusogenic agent can be a polymer, preferably a polyamino chain, *e.g.*,  
15 polyethyleneimine (PEI). The PEI can be linear, branched, synthetic or natural. The PEI can be, *e.g.*, alkyl substituted PEI, or lipid substituted PEI.

In other embodiments, the fusogenic agent can be polyhistidine, polyimidazole, polypyridine, polypropyleneimine, mellitin, or a polyacetal substance, *e.g.*, a cationic polyacetal. In some embodiment, the fusogenic agent can have an alpha helical structure.  
20 The fusogenic agent can be a membrane disruptive agent, *e.g.*, mellittin.

A fusogenic agent can have one or more of the following characteristics: (a) is at least 1Da in size; (b) has at least 10 charged groups, preferably between 10 and 5000 charged groups, more preferably between 50 and 1000 charged groups; (c) is present in the complex at a ratio of at least 1:1 fusogenic agent to carrier agent; (d) is present in the complex at a  
25 ratio of at least 1:1 fusogenic agent to condensing agent; (e) is present in the complex at a ratio of at least 1:1 fusogenic agent to targeting agent.

Other suitable fusogenic agents can be tested and identified by a skilled artisan. The ability of a compound to respond to, *e.g.*, change charge depending on, the pH environment can be tested by routine methods, *e.g.*, in a cellular assay. For example, a test compound is  
30 combined or contacted with a cell, and the cell is allowed to take up the test compound, *e.g.*, by endocytosis. An endosome preparation can then be made from the contacted cells and the

endosome preparation compared to an endosome preparation from control cells. A change, *e.g.*, a decrease, in the endosome fraction from the contacted cell vs. the control cell indicates that the test compound can function as a fusogenic agent. Alternatively, the contacted cell and control cell can be evaluated, *e.g.*, by microscopy, *e.g.*, by light or electron microscopy, to determine a difference in endosome population in the cells. The test compound can be labeled. In another type of assay, a modular complex described herein is constructed using one or more test or putative fusogenic agents. The modular complex can be constructed using a labeled nucleic acid instead of the iRNA. The ability of the fusogenic agent to respond to, *e.g.*, change charge depending on, the pH environment, once the modular complex is taken up by the cell, can be evaluated, *e.g.*, by preparation of an endosome preparation, or by microscopy techniques, as described above. A two-step assay can also be performed, wherein a first assay evaluates the ability of a test compound alone to respond to, *e.g.*, change charge depending on, the pH environment; and a second assay evaluates the ability of a modular complex that includes the test compound to respond to, *e.g.*, change charge depending on, the pH environment.

#### *Condensing agent*

The condensing agent of a modular complex described herein can interact with (*e.g.*, attracts, holds, or binds to) an iRNA agent and act to (a) condense, *e.g.*, reduce the size or charge of the iRNA agent and/or (b) protect the iRNA agent, *e.g.*, protect the iRNA agent against degradation. The condensing agent can include a moiety, *e.g.*, a charged moiety, that can interact with a nucleic acid, *e.g.*, an iRNA agent, *e.g.*, by ionic interactions. The condensing agent would preferably be a charged polymer, *e.g.*, a polycationic chain. The condensing agent can be a polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quarternary salt of a polyamine, or an alpha helical peptide.

A condensing agent can have the following characteristics: (a) at least 1Da in size; (b) has at least 2 charged groups, preferably between 2 and 100 charged groups; (c) is present in the complex at a ratio of at least 1:1 condensing agent to carrier agent; (d) is present in the



complex at a ratio of at least 1:1 condensing agent to fusogenic agent; (e) is present in the complex at a ratio of at least 1:1 condensing agent to targeting agent.

Other suitable condensing agents can be tested and identified by a skilled artisan, *e.g.*, by evaluating the ability of a test agent to interact with a nucleic acid, *e.g.*, an iRNA agent.

5 The ability of a test agent to interact with a nucleic acid, *e.g.*, an iRNA agent, *e.g.*, to condense or protect the iRNA agent, can be evaluated by routine techniques. In one assay, a test agent is contacted with a nucleic acid, and the size and/or charge of the contacted nucleic acid is evaluated by a technique suitable to detect changes in molecular mass and/or charge. Such techniques include non-denaturing gel electrophoresis, immunological methods, *e.g.*,  
10 immunoprecipitation, gel filtration, ionic interaction chromatography, and the like. A test agent is identified as a condensing agent if it changes the mass and/or charge (preferably both) of the contacted nucleic acid, compared to a control. A two-step assay can also be performed, wherein a first assay evaluates the ability of a test compound alone to interact with, *e.g.*, bind to, *e.g.*, condense the charge and/or mass of, a nucleic acid; and a second assay  
15 evaluates the ability of a modular complex that includes the test compound to interact with, *e.g.*, bind to, *e.g.*, condense the charge and/or mass of, a nucleic acid.

### **Amphipathic Delivery Agents**

In one aspect, the invention features an amphipathic delivery conjugate or module,  
20 such as those described herein and those described in copending, co-owned United States Provisional Application Serial No. 60/455,050 (Attorney Docket No. 14174-065P01), filed on March 13, 2003, which is hereby incorporated by reference.

In addition, the invention include an iRNA agent described herein, *e.g.*, a palindromic iRNA agent, an iRNA agent having a non canonical pairing, an iRNA agent which targets a  
25 gene described herein, *e.g.*, a gene active in the liver, an iRNA agent having a chemical modification described herein, *e.g.*, a modification which enhances resistance to degradation, an iRNA agent having an architecture or structure described herein, an iRNA agent administered as described herein, or an iRNA agent formulated as described herein, combined with, associated with, and delivered by such an amphipathic delivery conjugate.

30 An amphipathic molecule is a molecule having a hydrophobic and a hydrophilic region. Such molecules can interact with (*e.g.*, penetrate or disrupt) lipids, *e.g.*, a lipid



bylayer of a cell. As such, they can serve as delivery agent for an associated (e.g., bound) iRNA (e.g., an iRNA or sRNA described herein). A preferred amphipathic molecule to be used in the compositions described herein (e.g., the amphipathic iRNA constructs described herein) is a polymer. The polymer may have a secondary structure, e.g., a repeating  
5 secondary structure.

One example of an amphipathic polymer is an amphipathic polypeptide, e.g., a polypeptide having a secondary structure such that the polypeptide has a hydrophilic and a hydrophobic face. The design of amphipathic peptide structures (e.g., alpha-helical polypeptides) is routine to one of skill in the art. For example, the following references  
10 provide guidance: Grell et al. (2001) *Protein design and folding: template trapping of self-assembled helical bundles* J Pept Sci 7(3):146-51; Chen et al. (2002) *Determination of stereochemistry stability coefficients of amino acid side-chains in an amphipathic alpha-helix* J Pept Res 59(1):18-33; Iwata et al. (1994) *Design and synthesis of amphipathic 3(10)-helical peptides and their interactions with phospholipid bilayers and ion channel formation* J Biol  
15 Chem 269(7):4928-33; Cornut et al. (1994) *The amphipathic alpha-helix concept. Application to the de novo design of ideally amphipathic Leu, Lys peptides with hemolytic activity higher than that of melittin* FEBS Lett 349(1):29-33; Negrete et al. (1998) *Deciphering the structural code for proteins: helical propensities in domain classes and statistical multiresidue information in alpha-helices*. Protein Sci 7(6):1368-79.

20 Another example of an amphipathic polymer is a polymer made up of two or more amphipathic subunits, e.g., two or more subunits containing cyclic moieties (e.g., a cyclic moiety having one or more hydrophilic groups and one or more hydrophobic groups). For example, the subunit may contain a steroid, e.g., cholic acid; or an aromatic moiety. Such moieties preferably can exhibit atropisomerism, such that they can form opposing  
25 hydrophobic and hydrophilic faces when in a polymer structure.

The ability of a putative amphipathic molecule to interact with a lipid membrane, e.g., a cell membrane, can be tested by routine methods, e.g., in a cell free or cellular assay. For example, a test compound is combined or contacted with a synthetic lipid bilayer, a cellular membrane fraction, or a cell, and the test compound is evaluated for its ability to interact  
30 with, penetrate or disrupt the lipid bilayer, cell membrane or cell. The test compound can be labeled in order to detect the interaction with the lipid bilayer, cell membrane or cell. In

another type of assay, the test compound is linked to a reporter molecule or an iRNA agent (e.g., an iRNA or sRNA described herein) and the ability of the reporter molecule or iRNA agent to penetrate the lipid bilayer, cell membrane or cell is evaluated. A two-step assay can also be performed, wherein a first assay evaluates the ability of a test compound alone to  
5 interact with a lipid bilayer, cell membrane or cell; and a second assay evaluates the ability of a construct (e.g., a construct described herein) that includes the test compound and a reporter or iRNA agent to interact with a lipid bilayer, cell membrane or cell.

An amphipathic polymer useful in the compositions described herein has at least 2, preferably at least 5, more preferably at least 10, 25, 50, 100, 200, 500, 1000, 2000, 50000 or  
10 more subunits (e.g., amino acids or cyclic subunits). A single amphipathic polymer can be linked to one or more, e.g., 2, 3, 5, 10 or more iRNA agents (e.g., iRNA or sRNA agents described herein). In some embodiments, an amphipathic polymer can contain both amino acid and cyclic subunits, e.g., aromatic subunits.

The invention features a composition that includes an iRNA agent (e.g., an iRNA or  
15 sRNA described herein) in association with an amphipathic molecule. Such compositions may be referred to herein as "amphipathic iRNA constructs." Such compositions and constructs are useful in the delivery or targeting of iRNA agents, e.g., delivery or targeting of iRNA agents to a cell. While not wanting to be bound by theory, such compositions and constructs can increase the porosity of, e.g., can penetrate or disrupt, a lipid (e.g., a lipid  
20 bilayer of a cell), e.g., to allow entry of the iRNA agent into a cell.

In one aspect, the invention relates to a composition comprising an iRNA agent (e.g., an iRNA or sRNA agent described herein) linked to an amphipathic molecule. The iRNA agent and the amphipathic molecule may be held in continuous contact with one another by either covalent or noncovalent linkages.

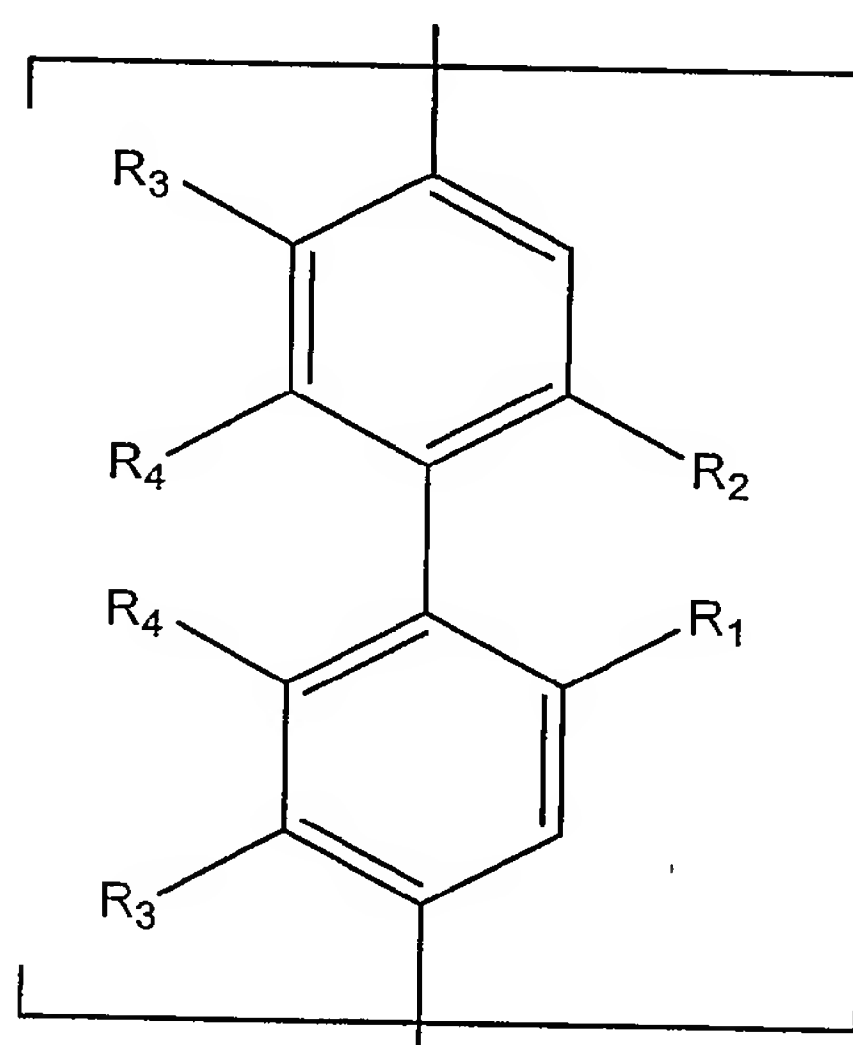
25 The amphipathic molecule of the composition or construct is preferably other than a phospholipid, e.g., other than a micelle, membrane or membrane fragment.

The amphipathic molecule of the composition or construct is preferably a polymer. The polymer may include two or more amphipathic subunits. One or more hydrophilic groups and one or more hydrophobic groups may be present on the polymer. The polymer  
30 may have a repeating secondary structure as well as a first face and a second face. The distribution of the hydrophilic groups and the hydrophobic groups along the repeating

secondary structure can be such that one face of the polymer is a hydrophilic face and the other face of the polymer is a hydrophobic face.

The amphipathic molecule can be a polypeptide, e.g., a polypeptide comprising an  $\alpha$ -helical conformation as its secondary structure.

5 In one embodiment, the amphipathic polymer includes one or more subunits containing one or more cyclic moiety (e.g., a cyclic moiety having one or more hydrophilic groups and/or one or more hydrophobic groups). In one embodiment, the polymer is a polymer of cyclic moieties such that the moieties have alternating hydrophobic and hydrophilic groups. For example, the subunit may contain a steroid, e.g., cholic acid. In  
10 another example, the subunit may contain an aromatic moiety. The aromatic moiety may be one that can exhibit atropisomerism, e.g., a 2,2'-bis(substituted)-1-1'-binaphthyl or a 2,2'-bis(substituted) biphenyl. A subunit may include an aromatic moiety of Formula (M):



(M)

15 The invention features a composition that includes an iRNA agent (e.g., an iRNA or sRNA described herein) in association with an amphipathic molecule. Such compositions may be referred to herein as "amphipathic iRNA constructs." Such compositions and constructs are useful in the delivery or targeting of iRNA agents, e.g., delivery or targeting  
20 of iRNA agents to a cell. While not wanting to be bound by theory, such compositions and

constructs can increase the porosity of, e.g., can penetrate or disrupt, a lipid (e.g., a lipid bilayer of a cell), e.g., to allow entry of the iRNA agent into a cell.

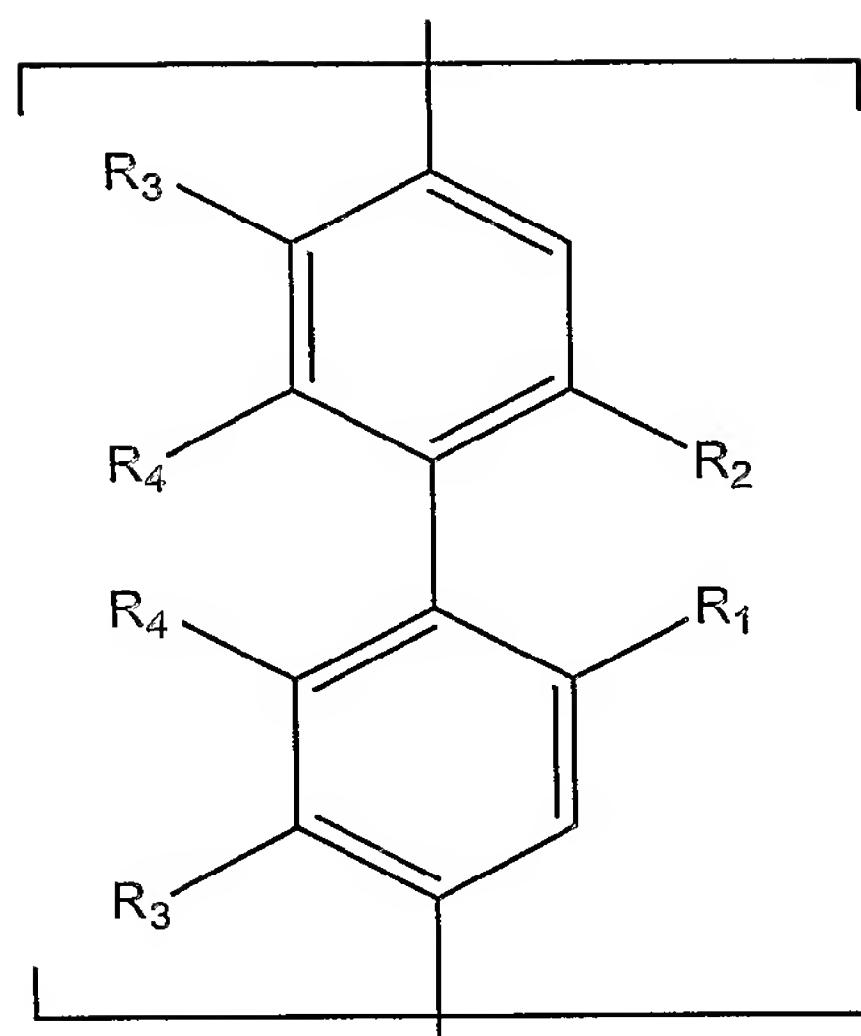
In one aspect, the invention relates to a composition comprising an iRNA agent (e.g., an iRNA or sRNA agent described herein) linked to an amphipathic molecule. The iRNA  
5 agent and the amphipathic molecule may be held in continuous contact with one another by either covalent or noncovalent linkages.

The amphipathic molecule of the composition or construct is preferably other than a phospholipid, e.g., other than a micelle, membrane or membrane fragment.

The amphipathic molecule of the composition or construct is preferably a polymer.  
10 The polymer may include two or more amphipathic subunits. One or more hydrophilic groups and one or more hydrophobic groups may be present on the polymer. The polymer may have a repeating secondary structure as well as a first face and a second face. The distribution of the hydrophilic groups and the hydrophobic groups along the repeating secondary structure can be such that one face of the polymer is a hydrophilic face and the  
15 other face of the polymer is a hydrophobic face.

The amphipathic molecule can be a polypeptide, e.g., a polypeptide comprising an  $\alpha$ -helical conformation as its secondary structure.

In one embodiment, the amphipathic polymer includes one or more subunits containing one or more cyclic moiety (e.g., a cyclic moiety having one or more hydrophilic  
20 groups and/or one or more hydrophobic groups). In one embodiment, the polymer is a polymer of cyclic moieties such that the moieties have alternating hydrophobic and hydrophilic groups. For example, the subunit may contain a steroid, e.g., cholic acid. In another example, the subunit may contain an aromatic moiety. The aromatic moiety may be one that can exhibit atropisomerism, e.g., a 2,2'-bis(substituted)-1-1'-binaphthyl or a 2,2'-  
25 bis(substituted) biphenyl. A subunit may include an aromatic moiety of Formula (M):



(M)

5

Referring to Formula M,  $R_1$  is  $C_1$ - $C_{100}$  alkyl optionally substituted with aryl, alkenyl, alkynyl, alkoxy or halo and/or optionally inserted with O, S, alkenyl or alkynyl;  $C_1$ - $C_{100}$  perfluoroalkyl; or  $OR_5$ .

$R_2$  is hydroxy; nitro; sulfate; phosphate; phosphate ester; sulfonic acid;  $OR_6$ ; or  $C_1$ - $C_{100}$  alkyl optionally substituted with hydroxy, halo, nitro, aryl or alkyl sulfinyl, aryl or alkyl sulfonyl, sulfate, sulfonic acid, phosphate, phosphate ester, substituted or unsubstituted aryl, carboxyl, carboxylate, amino carbonyl, or alkoxycarbonyl, and/or optionally inserted with O, NH, S,  $S(O)$ ,  $SO_2$ , alkenyl, or alkynyl.

$R_3$  is hydrogen, or when taken together with  $R_4$  forms a fused phenyl ring.

$R_4$  is hydrogen, or when taken together with  $R_3$  forms a fused phenyl ring.

$R_5$  is  $C_1$ - $C_{100}$  alkyl optionally substituted with aryl, alkenyl, alkynyl, alkoxy or halo and/or optionally inserted with O, S, alkenyl or alkynyl; or  $C_1$ - $C_{100}$  perfluoroalkyl; and  $R_6$  is  $C_1$ - $C_{100}$  alkyl optionally substituted with hydroxy, halo, nitro, aryl or alkyl sulfinyl, aryl or alkyl sulfonyl, sulfate, sulfonic acid, phosphate, phosphate ester, substituted or unsubstituted



aryl, carboxyl, carboxylate, amino carbonyl, or alkoxycarbonyl, and/or optionally inserted with O, NH, S, S(O), SO<sub>2</sub>, alkenyl, or alkynyl.

#### Increasing cellular uptake of dsRNAs

5 A method of the invention that can include the administration of an iRNA agent and a drug that affects the uptake of the iRNA agent into the cell. The drug can be administered before, after, or at the same time that the iRNA agent is administered. The drug can be covalently linked to the iRNA agent. The drug can be, for example, a lipopolysaccharide, an activator of p38 MAP kinase, or an activator of NF- $\kappa$ B. The drug can have a transient effect  
10 on the cell.

The drug can increase the uptake of the iRNA agent into the cell, for example, by disrupting the cell's cytoskeleton, *e.g.*, by disrupting the cell's microtubules, microfilaments, and/or intermediate filaments. The drug can be, for example, taxon, vincristine, vinblastine, cytochalasin, nocodazole, japlakinolide, latrunculin A, phalloidin, swinholide A, indanocine,  
15 or myoservin.

The drug can also increase the uptake of the iRNA agent into the cell by activating an inflammatory response, for example. Exemplary drug's that would have such an effect include tumor necrosis factor alpha (TNFalpha), interleukin-1 beta, or gamma interferon.

#### 20 iRNA conjugates

An iRNA agent can be coupled, *e.g.*, covalently coupled, to a second agent. For example, an iRNA agent used to treat a particular disorder can be coupled to a second therapeutic agent, *e.g.*, an agent other than the iRNA agent. The second therapeutic agent can be one which is directed to the treatment of the same disorder. For example, in the case  
25 of an iRNA used to treat a disorder characterized by unwanted cell proliferation, *e.g.*, cancer, the iRNA agent can be coupled to a second agent which has an anti-cancer effect. For example, it can be coupled to an agent which stimulates the immune system, *e.g.*, a CpG motif, or more generally an agent that activates a toll-like receptor and/or increases the production of gamma interferon.

30

## **iRNA Production**

An iRNA can be produced, *e.g.*, in bulk, by a variety of methods. Exemplary methods include: organic synthesis and RNA cleavage, *e.g.*, *in vitro* cleavage.

### 5       **Organic Synthesis**

An iRNA can be made by separately synthesizing each respective strand of a double-stranded RNA molecule. The component strands can then be annealed.

A large bioreactor, *e.g.*, the OligoPilot II from Pharmacia Biotec AB (Uppsala Sweden), can be used to produce a large amount of a particular RNA strand for a given  
10 iRNA. The OligoPilotII reactor can efficiently couple a nucleotide using only a 1.5 molar excess of a phosphoramidite nucleotide. To make an RNA strand, ribonucleotides amidites are used. Standard cycles of monomer addition can be used to synthesize the 21 to 23 nucleotide strand for the iRNA. Typically, the two complementary strands are produced separately and then annealed, *e.g.*, after release from the solid support and deprotection.

15       Organic synthesis can be used to produce a discrete iRNA species. The complementary of the species to a particular target gene can be precisely specified. For example, the species may be complementary to a region that includes a polymorphism, *e.g.*, a single nucleotide polymorphism. Further the location of the polymorphism can be precisely defined. In some embodiments, the polymorphism is located in an internal region, *e.g.*, at  
20       least 4, 5, 7, or 9 nucleotides from one or both of the termini.

### **dsRNA Cleavage**

iRNAs can also be made by cleaving a larger ds iRNA. The cleavage can be mediated *in vitro* or *in vivo*. For example, to produce iRNAs by cleavage *in vitro*, the following method can be used:

25       *In vitro* transcription. dsRNA is produced by transcribing a nucleic acid (DNA) segment in both directions. For example, the HiScribe™ RNAi transcription kit (New England Biolabs) provides a vector and a method for producing a dsRNA for a nucleic acid segment that is cloned into the vector at a position flanked on either side by a T7 promoter. Separate templates are generated for T7 transcription of the two complementary strands for  
30       the dsRNA. The templates are transcribed *in vitro* by addition of T7 RNA polymerase and

dsRNA is produced. Similar methods using PCR and/or other RNA polymerases (*e.g.*, T3 or SP6 polymerase) can also be used. In one embodiment, RNA generated by this method is carefully purified to remove endotoxins that may contaminate preparations of the recombinant enzymes.

5           *In vitro* cleavage. dsRNA is cleaved *in vitro* into iRNAs, for example, using a Dicer or comparable RNase III-based activity. For example, the dsRNA can be incubated in an *in vitro* extract from *Drosophila* or using purified components, *e.g.* a purified RNase or RISC complex (RNA-induced silencing complex). See, *e.g.*, Ketting *et al. Genes Dev* 2001 Oct 15;15(20):2654-9. and Hammond *Science* 2001 Aug 10;293(5532):1146-50.

10           dsRNA cleavage generally produces a plurality of iRNA species, each being a particular 21 to 23 nt fragment of a source dsRNA molecule. For example, iRNAs that include sequences complementary to overlapping regions and adjacent regions of a source dsRNA molecule may be present.

          Regardless of the method of synthesis, the iRNA preparation can be prepared in a  
15   solution (*e.g.*, an aqueous and/or organic solution) that is appropriate for formulation. For example, the iRNA preparation can be precipitated and redissolved in pure double-distilled water, and lyophilized. The dried iRNA can then be resuspended in a solution appropriate for the intended formulation process.

          Synthesis of modified and nucleotide surrogate iRNA agents is discussed below.

## 20           FORMULATION

          The iRNA agents described herein can be formulated for administration to a subject

          For ease of exposition the formulations, compositions and methods in this section are discussed largely with regard to unmodified iRNA agents. It should be understood, however, that these formulations, compositions and methods can be practiced with other iRNA agents,  
25   *e.g.*, modified iRNA agents, and such practice is within the invention.

          A formulated iRNA composition can assume a variety of states. In some examples, the composition is at least partially crystalline, uniformly crystalline, and/or anhydrous (*e.g.*, less than 80, 50, 30, 20, or 10% water). In another example, the iRNA is in an aqueous phase, *e.g.*, in a solution that includes water.

30           The aqueous phase or the crystalline compositions can, *e.g.*, be incorporated into a delivery vehicle, *e.g.*, a liposome (particularly for the aqueous phase) or a particle (*e.g.*, a

microparticle as can be appropriate for a crystalline composition). Generally, the iRNA composition is formulated in a manner that is compatible with the intended method of administration (see, below).

5 In particular embodiments, the composition is prepared by at least one of the following methods: spray drying, lyophilization, vacuum drying, evaporation, fluid bed drying, or a combination of these techniques; or sonication with a lipid, freeze-drying, condensation and other self-assembly.

A iRNA preparation can be formulated in combination with another agent, *e.g.*, another therapeutic agent or an agent that stabilizes a iRNA, *e.g.*, a protein that complexes  
10 with iRNA to form an iRNP. Still other agents include chelators, *e.g.*, EDTA (*e.g.*, to remove divalent cations such as  $Mg^{2+}$ ), salts, RNase inhibitors (*e.g.*, a broad specificity RNase inhibitor such as RNasin) and so forth.

In one embodiment, the iRNA preparation includes another iRNA agent, *e.g.*, a second iRNA that can mediated RNAi with respect to a second gene, or with respect to the  
15 same gene. Still other preparation can include at least 3, 5, ten, twenty, fifty, or a hundred or more different iRNA species. Such iRNAs can mediated RNAi with respect to a similar number of different genes.

In one embodiment, the iRNA preparation includes at least a second therapeutic agent (*e.g.*, an agent other than an RNA or a DNA). For example, a iRNA composition for the  
20 treatment of a viral disease, *e.g.* HIV, might include a known antiviral agent (*e.g.*, a protease inhibitor or reverse transcriptase inhibitor). In another example, a iRNA composition for the treatment of a cancer might further comprise a chemotherapeutic agent.

Exemplary formulations are discussed below:

### Liposomes

25 For ease of exposition the formulations, compositions and methods in this section are discussed largely with regard to unmodified iRNA agents. It should be understood, however, that these formulations, compositions and methods can be practiced with other iRNA agents, *e.g.*, modified iRNA s agents, and such practice is within the invention. An iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA  
30 agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) preparation can be

formulated for delivery in a membranous molecular assembly, *e.g.*, a liposome or a micelle. As used herein, the term “liposome” refers to a vesicle composed of amphiphilic lipids arranged in at least one bilayer, *e.g.*, one bilayer or a plurality of bilayers. Liposomes include unilamellar and multilamellar vesicles that have a membrane formed from a lipophilic material and an aqueous interior. The aqueous portion contains the iRNA composition. The lipophilic material isolates the aqueous interior from an aqueous exterior, which typically does not include the iRNA composition, although in some examples, it may. Liposomes are useful for the transfer and delivery of active ingredients to the site of action. Because the liposomal membrane is structurally similar to biological membranes, when liposomes are applied to a tissue, the liposomal bilayer fuses with bilayer of the cellular membranes. As the merging of the liposome and cell progresses, the internal aqueous contents that include the iRNA are delivered into the cell where the iRNA can specifically bind to a target RNA and can mediate RNAi. In some cases the liposomes are also specifically targeted, *e.g.*, to direct the iRNA to particular cell types.

A liposome containing a iRNA can be prepared by a variety of methods.

In one example, the lipid component of a liposome is dissolved in a detergent so that micelles are formed with the lipid component. For example, the lipid component can be an amphipathic cationic lipid or lipid conjugate. The detergent can have a high critical micelle concentration and may be nonionic. Exemplary detergents include cholate, CHAPS, octylglucoside, deoxycholate, and lauroyl sarcosine. The iRNA preparation is then added to the micelles that include the lipid component. The cationic groups on the lipid interact with the iRNA and condense around the iRNA to form a liposome. After condensation, the detergent is removed, *e.g.*, by dialysis, to yield a liposomal preparation of iRNA.

If necessary a carrier compound that assists in condensation can be added during the condensation reaction, *e.g.*, by controlled addition. For example, the carrier compound can be a polymer other than a nucleic acid (*e.g.*, spermine or spermidine). pH can also adjusted to favor condensation.

Further description of methods for producing stable polynucleotide delivery vehicles, which incorporate a polynucleotide/cationic lipid complex as structural components of the delivery vehicle, are described in, *e.g.*, WO 96/37194. Liposome formation can also include one or more aspects of exemplary methods described in Felgner, P. L. *et al.*, *Proc. Natl.*



*Acad. Sci.*, USA 8:7413-7417, 1987; U.S. Pat. No. 4,897,355; U.S. Pat. No. 5,171,678; Bangham, *et al. M. Mol. Biol.* 23:238, 1965; Olson, *et al. Biochim. Biophys. Acta* 557:9, 1979; Szoka, *et al. Proc. Natl. Acad. Sci.* 75: 4194, 1978; Mayhew, *et al. Biochim. Biophys. Acta* 775:169, 1984; Kim, *et al. Biochim. Biophys. Acta* 728:339, 1983; and Fukunaga, *et al. Endocrinol.* 115:757, 1984. Commonly used techniques for preparing lipid aggregates of appropriate size for use as delivery vehicles include sonication and freeze-thaw plus extrusion (see, *e.g.*, Mayer, *et al. Biochim. Biophys. Acta* 858:161, 1986). Microfluidization can be used when consistently small (50 to 200 nm) and relatively uniform aggregates are desired (Mayhew, *et al. Biochim. Biophys. Acta* 775:169, 1984). These methods are readily adapted to packaging iRNA preparations into liposomes.

Liposomes that are pH-sensitive or negatively-charged, entrap nucleic acid molecules rather than complex with them. Since both the nucleic acid molecules and the lipid are similarly charged, repulsion rather than complex formation occurs. Nevertheless, some nucleic acid molecules are entrapped within the aqueous interior of these liposomes. pH-sensitive liposomes have been used to deliver DNA encoding the thymidine kinase gene to cell monolayers in culture. Expression of the exogenous gene was detected in the target cells (Zhou *et al.*, *Journal of Controlled Release*, 19, (1992) 269-274).

One major type of liposomal composition includes phospholipids other than naturally-derived phosphatidylcholine. Neutral liposome compositions, for example, can be formed from dimyristoyl phosphatidylcholine (DMPC) or dipalmitoyl phosphatidylcholine (DPPC). Anionic liposome compositions generally are formed from dimyristoyl phosphatidylglycerol, while anionic fusogenic liposomes are formed primarily from dioleoyl phosphatidylethanolamine (DOPE). Another type of liposomal composition is formed from phosphatidylcholine (PC) such as, for example, soybean PC, and egg PC. Another type is formed from mixtures of phospholipid and/or phosphatidylcholine and/or cholesterol.

Examples of other methods to introduce liposomes into cells *in vitro* and *in vivo* include U.S. Pat. No. 5,283,185; U.S. Pat. No. 5,171,678; WO 94/00569; WO 93/24640; WO 91/16024; Felgner, *J. Biol. Chem.* 269:2550, 1994; Nabel, *Proc. Natl. Acad. Sci.* 90:11307, 1993; Nabel, *Human Gene Ther.* 3:649, 1992; Gershon, *Biochem.* 32:7143, 1993; and Strauss *EMBO J.* 11:417, 1992.

In one embodiment, cationic liposomes are used. Cationic liposomes possess the advantage of being able to fuse to the cell membrane. Non-cationic liposomes, although not able to fuse as efficiently with the plasma membrane, are taken up by macrophages *in vivo* and can be used to deliver iRNAs to macrophages.

5 Further advantages of liposomes include: liposomes obtained from natural phospholipids are biocompatible and biodegradable; liposomes can incorporate a wide range of water and lipid soluble drugs; liposomes can protect encapsulated iRNAs in their internal compartments from metabolism and degradation (Rosoff, in "Pharmaceutical Dosage Forms," Lieberman, Rieger and Banker (Eds.), 1988, volume 1, p. 245). Important  
10 considerations in the preparation of liposome formulations are the lipid surface charge, vesicle size and the aqueous volume of the liposomes.

A positively charged synthetic cationic lipid, N-[1-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA) can be used to form small liposomes that interact spontaneously with nucleic acid to form lipid-nucleic acid complexes which are capable of  
15 fusing with the negatively charged lipids of the cell membranes of tissue culture cells, resulting in delivery of iRNA (see, *e.g.*, Felgner, P. L. *et al.*, Proc. Natl. Acad. Sci., USA 8:7413-7417, 1987 and U.S. Pat. No. 4,897,355 for a description of DOTMA and its use with DNA).

A DOTMA analogue, 1,2-bis(oleoyloxy)-3-(trimethylammonia)propane (DOTAP)  
20 can be used in combination with a phospholipid to form DNA-complexing vesicles. Lipofectin™ (Bethesda Research Laboratories, Gaithersburg, Md.) is an effective agent for the delivery of highly anionic nucleic acids into living tissue culture cells that comprise positively charged DOTMA liposomes which interact spontaneously with negatively charged polynucleotides to form complexes. When enough positively charged liposomes are used,  
25 the net charge on the resulting complexes is also positive. Positively charged complexes prepared in this way spontaneously attach to negatively charged cell surfaces, fuse with the plasma membrane, and efficiently deliver functional nucleic acids into, for example, tissue culture cells. Another commercially available cationic lipid, 1,2-bis(oleoyloxy)-3,3-(trimethylammonia)propane ("DOTAP") (Boehringer Mannheim, Indianapolis, Indiana)  
30 differs from DOTMA in that the oleoyl moieties are linked by ester, rather than ether linkages.

Other reported cationic lipid compounds include those that have been conjugated to a variety of moieties including, for example, carboxyspermine which has been conjugated to one of two types of lipids and includes compounds such as 5-carboxyspermylglycine dioctaoyleamide ("DOGS") (Transfectam™, Promega, Madison, Wisconsin) and  
5 dipalmitoylphosphatidylethanolamine 5-carboxyspermyl-amide ("DPPES") (see, *e.g.*, U.S. Pat. No. 5,171,678).

Another cationic lipid conjugate includes derivatization of the lipid with cholesterol ("DC-Chol") which has been formulated into liposomes in combination with DOPE (See, Gao, X. and Huang, L., *Biochim. Biophys. Res. Commun.* 179:280, 1991). Lipopolylysine,  
10 made by conjugating polylysine to DOPE, has been reported to be effective for transfection in the presence of serum (Zhou, X. *et al.*, *Biochim. Biophys. Acta* 1065:8, 1991). For certain cell lines, these liposomes containing conjugated cationic lipids, are said to exhibit lower toxicity and provide more efficient transfection than the DOTMA-containing compositions. Other commercially available cationic lipid products include DMRIE and DMRIE-HP  
15 (Vical, La Jolla, California) and Lipofectamine (DOSPA) (Life Technology, Inc., Gaithersburg, Maryland). Other cationic lipids suitable for the delivery of oligonucleotides are described in WO 98/39359 and WO 96/37194.

Liposomal formulations are particularly suited for topical administration, liposomes present several advantages over other formulations. Such advantages include reduced side  
20 effects related to high systemic absorption of the administered drug, increased accumulation of the administered drug at the desired target, and the ability to administer iRNA, into the skin. In some implementations, liposomes are used for delivering iRNA to epidermal cells and also to enhance the penetration of iRNA into dermal tissues, *e.g.*, into skin. For example, the liposomes can be applied topically. Topical delivery of drugs formulated as liposomes to  
25 the skin has been documented (see, *e.g.*, Weiner *et al.*, *Journal of Drug Targeting*, 1992, vol. 2, 405-410 and du Plessis *et al.*, *Antiviral Research*, 18, 1992, 259-265; Mannino, R. J. and Fould-Fogerite, S., *Biotechniques* 6:682-690, 1988; Itani, T. *et al.* *Gene* 56:267-276, 1987; Nicolau, C. *et al.* *Meth. Enz.* 149:157-176, 1987; Straubinger, R. M. and Papahadjopoulos, D. *Meth. Enz.* 101:512-527, 1983; Wang, C. Y. and Huang, L., *Proc. Natl. Acad. Sci. USA*  
30 84:7851-7855, 1987).

Non-ionic liposomal systems have also been examined to determine their utility in the delivery of drugs to the skin, in particular systems comprising non-ionic surfactant and cholesterol. Non-ionic liposomal formulations comprising Novasome I (glyceryl dilaurate/cholesterol/polyoxyethylene-10-stearyl ether) and Novasome II (glyceryl distearate/cholesterol/polyoxyethylene-10-stearyl ether) were used to deliver a drug into the dermis of mouse skin. Such formulations with iRNA are useful for treating a dermatological disorder.

Liposomes that include iRNA can be made highly deformable. Such deformability can enable the liposomes to penetrate through pore that are smaller than the average radius of the liposome. For example, transfersomes are a type of deformable liposomes. Transfersomes can be made by adding surface edge activators, usually surfactants, to a standard liposomal composition. Transfersomes that include iRNA can be delivered, for example, subcutaneously by infection in order to deliver iRNA to keratinocytes in the skin. In order to cross intact mammalian skin, lipid vesicles must pass through a series of fine pores, each with a diameter less than 50 nm, under the influence of a suitable transdermal gradient. In addition, due to the lipid properties, these transfersomes can be self-optimizing (adaptive to the shape of pores, *e.g.*, in the skin), self-repairing, and can frequently reach their targets without fragmenting, and often self-loading. The iRNA agents can include an RRMS tethered to a moiety which improves association with a liposome.

### Surfactants

For ease of exposition the formulations, compositions and methods in this section are discussed largely with regard to unmodified iRNA agents. It should be understood, however, that these formulations, compositions and methods can be practiced with other iRNA agents, *e.g.*, modified iRNA agents, and such practice is within the invention. Surfactants find wide application in formulations such as emulsions (including microemulsions) and liposomes (see above). iRNA (or a precursor, *e.g.*, a larger dsRNA which can be processed into a iRNA, or a DNA which encodes a iRNA or precursor) compositions can include a surfactant. In one embodiment, the iRNA is formulated as an emulsion that includes a surfactant. The most common way of classifying and ranking the properties of the many different types of surfactants, both natural and synthetic, is by the use of the hydrophile/lipophile balance (HLB). The nature of the hydrophilic group provides the most useful means for categorizing



the different surfactants used in formulations (Rieger, in "Pharmaceutical Dosage Forms," Marcel Dekker, Inc., New York, NY, 1988, p. 285).

If the surfactant molecule is not ionized, it is classified as a nonionic surfactant. Nonionic surfactants find wide application in pharmaceutical products and are usable over a wide range of pH values. In general their HLB values range from 2 to about 18 depending on their structure. Nonionic surfactants include nonionic esters such as ethylene glycol esters, propylene glycol esters, glyceryl esters, polyglyceryl esters, sorbitan esters, sucrose esters, and ethoxylated esters. Nonionic alkanolamides and ethers such as fatty alcohol ethoxylates, propoxylated alcohols, and ethoxylated/propoxylated block polymers are also included in this class. The polyoxyethylene surfactants are the most popular members of the nonionic surfactant class.

If the surfactant molecule carries a negative charge when it is dissolved or dispersed in water, the surfactant is classified as anionic. Anionic surfactants include carboxylates such as soaps, acyl lactylates, acyl amides of amino acids, esters of sulfuric acid such as alkyl sulfates and ethoxylated alkyl sulfates, sulfonates such as alkyl benzene sulfonates, acyl isethionates, acyl taurates and sulfosuccinates, and phosphates. The most important members of the anionic surfactant class are the alkyl sulfates and the soaps.

If the surfactant molecule carries a positive charge when it is dissolved or dispersed in water, the surfactant is classified as cationic. Cationic surfactants include quaternary ammonium salts and ethoxylated amines. The quaternary ammonium salts are the most used members of this class.

If the surfactant molecule has the ability to carry either a positive or negative charge, the surfactant is classified as amphoteric. Amphoteric surfactants include acrylic acid derivatives, substituted alkylamides, N-alkylbetaines and phosphatides.

The use of surfactants in drug products, formulations and in emulsions has been reviewed (Rieger, in "Pharmaceutical Dosage Forms," Marcel Dekker, Inc., New York, NY, 1988, p. 285).

#### Micelles and other Membranous Formulations

For ease of exposition the micelles and other formulations, compositions and methods in this section are discussed largely with regard to unmodified iRNA agents. It should be understood, however, that these micelles and other formulations, compositions and methods



can be practiced with other iRNA agents, *e.g.*, modified iRNA agents, and such practice is within the invention. The iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof)) composition can be provided as a micellar formulation. "Micelles" are defined herein as a particular type of molecular assembly in which amphipathic molecules are arranged in a spherical structure such that all the hydrophobic portions of the molecules are directed inward, leaving the hydrophilic portions in contact with the surrounding aqueous phase. The converse arrangement exists if the environment is hydrophobic.

10           A mixed micellar formulation suitable for delivery through transdermal membranes may be prepared by mixing an aqueous solution of the iRNA composition, an alkali metal C<sub>8</sub> to C<sub>22</sub> alkyl sulphate, and a micelle forming compounds. Exemplary micelle forming compounds include lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linoleic acid, 15   linolenic acid, monoolein, monooleates, monolaurates, borage oil, evening of primrose oil, menthol, trihydroxy oxo cholanyl glycine and pharmaceutically acceptable salts thereof, glycerin, polyglycerin, lysine, polylysine, triolein, polyoxyethylene ethers and analogues thereof, polidocanol alkyl ethers and analogues thereof, chenodeoxycholate, deoxycholate, and mixtures thereof. The micelle forming compounds may be added at the same time or 20   after addition of the alkali metal alkyl sulphate. Mixed micelles will form with substantially any kind of mixing of the ingredients but vigorous mixing is preferred in order to provide smaller size micelles.

          In one method a first micellar composition is prepared which contains the iRNA composition and at least the alkali metal alkyl sulphate. The first micellar composition is then 25   mixed with at least three micelle forming compounds to form a mixed micellar composition. In another method, the micellar composition is prepared by mixing the iRNA composition, the alkali metal alkyl sulphate and at least one of the micelle forming compounds, followed by addition of the remaining micelle forming compounds, with vigorous mixing.

          Phenol and/or m-cresol may be added to the mixed micellar composition to stabilize 30   the formulation and protect against bacterial growth. Alternatively, phenol and/or m-cresol

may be added with the micelle forming ingredients. An isotonic agent such as glycerin may also be added after formation of the mixed micellar composition.

For delivery of the micellar formulation as a spray, the formulation can be put into an aerosol dispenser and the dispenser is charged with a propellant. The propellant, which is  
5 under pressure, is in liquid form in the dispenser. The ratios of the ingredients are adjusted so that the aqueous and propellant phases become one, *i.e.* there is one phase. If there are two phases, it is necessary to shake the dispenser prior to dispensing a portion of the contents, *e.g.* through a metered valve. The dispensed dose of pharmaceutical agent is propelled from the metered valve in a fine spray.

10 The preferred propellants are hydrogen-containing chlorofluorocarbons, hydrogen-containing fluorocarbons, dimethyl ether and diethyl ether. Even more preferred is HFA 134a (1,1,1,2 tetrafluoroethane).

The specific concentrations of the essential ingredients can be determined by relatively straightforward experimentation. For absorption through the oral cavities, it is  
15 often desirable to increase, *e.g.* at least double or triple, the dosage for through injection or administration through the gastrointestinal tract.

The iRNA agents can include an RRMS tethered to a moiety which improves association with a micelle or other membranous formulation.

### Particles

20 For ease of exposition the particles, formulations, compositions and methods in this section are discussed largely with regard to unmodified iRNA agents. It should be understood, however, that these particles, formulations, compositions and methods can be practiced with other iRNA agents, *e.g.*, modified iRNA agents, and such practice is within the invention. In another embodiment, an iRNA agent, *e.g.*, a double-stranded iRNA agent,  
25 or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) preparations may be incorporated into a particle, *e.g.*, a microparticle. Microparticles can be produced by spray-drying, but may also be produced by other methods including lyophilization, evaporation, fluid bed drying, vacuum drying, or a  
30 combination of these techniques. See below for further description.

Sustained -Release Formulations. An iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) described herein can be formulated for  
5 controlled, *e.g.*, slow release. Controlled release can be achieved by disposing the iRNA within a structure or substance which impedes its release. *E.g.*, iRNA can be disposed within a porous matrix or in an erodable matrix, either of which allow release of the iRNA over a period of time.

Polymeric particles, *e.g.*, polymeric in microparticles can be used as a sustained-  
10 release reservoir of iRNA that is taken up by cells only released from the microparticle through biodegradation. The polymeric particles in this embodiment should therefore be large enough to preclude phagocytosis (*e.g.*, larger than 10  $\mu\text{m}$  and preferably larger than 20  $\mu\text{m}$ ). Such particles can be produced by the same methods to make smaller particles, but with less vigorous mixing of the first and second emulsions. That is to say, a lower  
15 homogenization speed, vortex mixing speed, or sonication setting can be used to obtain particles having a diameter around 100  $\mu\text{m}$  rather than 10  $\mu\text{m}$ . The time of mixing also can be altered.

Larger microparticles can be formulated as a suspension, a powder, or an implantable solid, to be delivered by intramuscular, subcutaneous, intradermal, intravenous, or  
20 intraperitoneal injection; via inhalation (intranasal or intrapulmonary); orally; or by implantation. These particles are useful for delivery of any iRNA when slow release over a relatively long term is desired. The rate of degradation, and consequently of release, varies with the polymeric formulation.

Microparticles preferably include pores, voids, hollows, defects or other interstitial  
25 spaces that allow the fluid suspension medium to freely permeate or perfuse the particulate boundary. For example, the perforated microstructures can be used to form hollow, porous spray dried microspheres.

Polymeric particles containing iRNA (*e.g.*, a sRNA) can be made using a double emulsion technique, for instance. First, the polymer is dissolved in an organic solvent. A  
30 preferred polymer is polylactic-co-glycolic acid (PLGA), with a lactic/glycolic acid weight ratio of 65:35, 50:50, or 75:25. Next, a sample of nucleic acid suspended in aqueous solution

is added to the polymer solution and the two solutions are mixed to form a first emulsion. The solutions can be mixed by vortexing or shaking, and in a preferred method, the mixture can be sonicated. Most preferable is any method by which the nucleic acid receives the least amount of damage in the form of nicking, shearing, or degradation, while still allowing the formation of an appropriate emulsion. For example, acceptable results can be obtained with a  
5 Vibra-cell model VC-250 sonicator with a 1/8" microtip probe, at setting #3.

**Spray-Drying.** An iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or  
10 precursor thereof)) can be prepared by spray drying. Spray dried iRNA can be administered to a subject or be subjected to further formulation. A pharmaceutical composition of iRNA can be prepared by spray drying a homogeneous aqueous mixture that includes a iRNA under conditions sufficient to provide a dispersible powdered composition, *e.g.*, a pharmaceutical composition. The material for spray drying can also include one or more of: a  
15 pharmaceutically acceptable excipient, or a dispersibility-enhancing amount of a physiologically acceptable, water-soluble protein. The spray-dried product can be a dispersible powder that includes the iRNA.

Spray drying is a process that converts a liquid or slurry material to a dried particulate form. Spray drying can be used to provide powdered material for various administrative  
20 routes including inhalation. See, for example, M. Sacchetti and M. M. Van Oort in: Inhalation Aerosols: Physical and Biological Basis for Therapy, A. J. Hickey, ed. Marcel Dekkar, New York, 1996.

Spray drying can include atomizing a solution, emulsion, or suspension to form a fine mist of droplets and drying the droplets. The mist can be projected into a drying chamber  
25 (*e.g.*, a vessel, tank, tubing, or coil) where it contacts a drying gas. The mist can include solid or liquid pore forming agents. The solvent and pore forming agents evaporate from the droplets into the drying gas to solidify the droplets, simultaneously forming pores throughout the solid. The solid (typically in a powder, particulate form) then is separated from the drying gas and collected.

30 Spray drying includes bringing together a highly dispersed liquid, and a sufficient volume of air (*e.g.*, hot air) to produce evaporation and drying of the liquid droplets. The



preparation to be spray dried can be any solution, course suspension, slurry, colloidal dispersion, or paste that may be atomized using the selected spray drying apparatus.

Typically, the feed is sprayed into a current of warm filtered air that evaporates the solvent and conveys the dried product to a collector. The spent air is then exhausted with the solvent.

5 Several different types of apparatus may be used to provide the desired product. For example, commercial spray dryers manufactured by Buchi Ltd. or Niro Corp. can effectively produce particles of desired size.

Spray-dried powdered particles can be approximately spherical in shape, nearly uniform in size and frequently hollow. There may be some degree of irregularity in shape  
10 depending upon the incorporated medicament and the spray drying conditions. In many instances the dispersion stability of spray-dried microspheres appears to be more effective if an inflating agent (or blowing agent) is used in their production. Particularly preferred embodiments may comprise an emulsion with an inflating agent as the disperse or continuous phase (the other phase being aqueous in nature). An inflating agent is preferably dispersed  
15 with a surfactant solution, using, for instance, a commercially available microfluidizer at a pressure of about 5000 to 15,000 psi. This process forms an emulsion, preferably stabilized by an incorporated surfactant, typically comprising submicron droplets of water immiscible blowing agent dispersed in an aqueous continuous phase. The formation of such dispersions using this and other techniques are common and well known to those in the art. The blowing  
20 agent is preferably a fluorinated compound (*e.g.* perfluorohexane, perfluorooctyl bromide, perfluorodecalin, perfluorobutyl ethane) which vaporizes during the spray-drying process, leaving behind generally hollow, porous aerodynamically light microspheres. As will be discussed in more detail below, other suitable blowing agents include chloroform, freons, and hydrocarbons. Nitrogen gas and carbon dioxide are also contemplated as a suitable blowing  
25 agent.

Although the perforated microstructures are preferably formed using a blowing agent as described above, it will be appreciated that, in some instances, no blowing agent is required and an aqueous dispersion of the medicament and surfactant(s) are spray dried directly. In such cases, the formulation may be amenable to process conditions (*e.g.*, elevated  
30 temperatures) that generally lead to the formation of hollow, relatively porous microparticles. Moreover, the medicament may possess special physicochemical properties (*e.g.*, high



crystallinity, elevated melting temperature, surface activity, etc.) that make it particularly suitable for use in such techniques.

The perforated microstructures may optionally be associated with, or comprise, one or more surfactants. Moreover, miscible surfactants may optionally be combined with the suspension medium liquid phase. It will be appreciated by those skilled in the art that the use of surfactants may further increase dispersion stability, simplify formulation procedures or increase bioavailability upon administration. Of course combinations of surfactants, including the use of one or more in the liquid phase and one or more associated with the perforated microstructures are contemplated as being within the scope of the invention. By “associated with or comprise” it is meant that the structural matrix or perforated microstructure may incorporate, adsorb, absorb, be coated with or be formed by the surfactant.

Surfactants suitable for use include any compound or composition that aids in the formation and maintenance of the stabilized respiratory dispersions by forming a layer at the interface between the structural matrix and the suspension medium. The surfactant may comprise a single compound or any combination of compounds, such as in the case of co-surfactants. Particularly preferred surfactants are substantially insoluble in the propellant, nonfluorinated, and selected from the group consisting of saturated and unsaturated lipids, nonionic detergents, nonionic block copolymers, ionic surfactants, and combinations of such agents. It should be emphasized that, in addition to the aforementioned surfactants, suitable (*i.e.* biocompatible) fluorinated surfactants are compatible with the teachings herein and may be used to provide the desired stabilized preparations.

Lipids, including phospholipids, from both natural and synthetic sources may be used in varying concentrations to form a structural matrix. Generally, compatible lipids comprise those that have a gel to liquid crystal phase transition greater than about 40° C. Preferably, the incorporated lipids are relatively long chain (*i.e.* C<sub>6</sub>-C<sub>22</sub>) saturated lipids and more preferably comprise phospholipids. Exemplary phospholipids useful in the disclosed stabilized preparations comprise egg phosphatidylcholine, dilauroylphosphatidylcholine, dioleoylphosphatidylcholine, dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, short-chain phosphatidylcholines, phosphatidylethanolamine, dioleoylphosphatidylethanolamine, phosphatidylserine, phosphatidylglycerol,

phosphatidylinositol, glycolipids, ganglioside GM1, sphingomyelin, phosphatidic acid, cardiolipin; lipids bearing polymer chains such as, polyethylene glycol, chitin, hyaluronic acid, or polyvinylpyrrolidone; lipids bearing sulfonated mono-, di-, and polysaccharides; fatty acids such as palmitic acid, stearic acid, and oleic acid; cholesterol, cholesterol esters, and cholesterol hemisuccinate. Due to their excellent biocompatibility characteristics, phospholipids and combinations of phospholipids and poloxamers are particularly suitable for use in the stabilized dispersions disclosed herein.

Compatible nonionic detergents comprise: sorbitan esters including sorbitan trioleate (Spans<sup>TM</sup> 85), sorbitan sesquioleate, sorbitan monooleate, sorbitan monolaurate, polyoxyethylene (20) sorbitan monolaurate, and polyoxyethylene (20) sorbitan monooleate, oleyl polyoxyethylene (2) ether, stearyl polyoxyethylene (2) ether, lauryl polyoxyethylene (4) ether, glycerol esters, and sucrose esters. Other suitable nonionic detergents can be easily identified using McCutcheon's Emulsifiers and Detergents (McPublishing Co., Glen Rock, N.J.). Preferred block copolymers include diblock and triblock copolymers of polyoxyethylene and polyoxypropylene, including poloxamer 188 (Pluronic.RTM. F68), poloxamer 407 (Pluronic.RTM. F-127), and poloxamer 338. Ionic surfactants such as sodium sulfosuccinate, and fatty acid soaps may also be utilized. In preferred embodiments, the microstructures may comprise oleic acid or its alkali salt.

In addition to the aforementioned surfactants, cationic surfactants or lipids are preferred especially in the case of delivery of an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof). Examples of suitable cationic lipids include: DOTMA, N-[-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium-chloride; DOTAP, 1,2-dioleyloxy-3-(trimethylammonio)propane; and DOTB, 1,2-dioleyl-3-(4'-trimethylammonio)butanoyl-sn-glycerol. Polycationic amino acids such as polylysine, and polyarginine are also contemplated.

For the spraying process, such spraying methods as rotary atomization, pressure atomization and two-fluid atomization can be used. Examples of the devices used in these processes include "Parubisu [phonetic rendering] Mini-Spray GA-32" and "Parubisu Spray Drier DL-41", manufactured by Yamato Chemical Co., or "Spray Drier CL-8," "Spray Drier

L-8,” “Spray Drier FL-12,” “Spray Drier FL-16” or “Spray Drier FL-20,” manufactured by Okawara Kakoki Co., can be used for the method of spraying using rotary-disk atomizer.

While no particular restrictions are placed on the gas used to dry the sprayed material, it is recommended to use air, nitrogen gas or an inert gas. The temperature of the inlet of the gas used to dry the sprayed materials such that it does not cause heat deactivation of the sprayed material. The range of temperatures may vary between about 50°C to about 200°C, preferably between about 50°C and 100°C. The temperature of the outlet gas used to dry the sprayed material, may vary between about 0°C and about 150°C, preferably between 0°C and 90°C, and even more preferably between 0°C and 60°C.

The spray drying is done under conditions that result in substantially amorphous powder of homogeneous constitution having a particle size that is respirable, a low moisture content and flow characteristics that allow for ready aerosolization. Preferably the particle size of the resulting powder is such that more than about 98% of the mass is in particles having a diameter of about 10 µm or less with about 90% of the mass being in particles having a diameter less than 5 µm. Alternatively, about 95% of the mass will have particles with a diameter of less than 10 µm with about 80% of the mass of the particles having a diameter of less than 5 µm.

The dispersible pharmaceutical-based dry powders that include the iRNA preparation may optionally be combined with pharmaceutical carriers or excipients which are suitable for respiratory and pulmonary administration. Such carriers may serve simply as bulking agents when it is desired to reduce the iRNA concentration in the powder which is being delivered to a patient, but may also serve to enhance the stability of the iRNA compositions and to improve the dispersibility of the powder within a powder dispersion device in order to provide more efficient and reproducible delivery of the iRNA and to improve handling characteristics of the iRNA such as flowability and consistency to facilitate manufacturing and powder filling.

Such carrier materials may be combined with the drug prior to spray drying, *i.e.*, by adding the carrier material to the purified bulk solution. In that way, the carrier particles will be formed simultaneously with the drug particles to produce a homogeneous powder. Alternatively, the carriers may be separately prepared in a dry powder form and combined with the dry powder drug by blending. The powder carriers will usually be crystalline (to

avoid water absorption), but might in some cases be amorphous or mixtures of crystalline and amorphous. The size of the carrier particles may be selected to improve the flowability of the drug powder, typically being in the range from 25  $\mu\text{m}$  to 100  $\mu\text{m}$ . A preferred carrier material is crystalline lactose having a size in the above-stated range.

5 Powders prepared by any of the above methods will be collected from the spray dryer in a conventional manner for subsequent use. For use as pharmaceuticals and other purposes, it will frequently be desirable to disrupt any agglomerates which may have formed by screening or other conventional techniques. For pharmaceutical uses, the dry powder formulations will usually be measured into a single dose, and the single dose sealed into a  
10 package. Such packages are particularly useful for dispersion in dry powder inhalers, as described in detail below. Alternatively, the powders may be packaged in multiple-dose containers.

Methods for spray drying hydrophobic and other drugs and components are described in U.S. Pat. Nos. 5,000,888; 5,026,550; 4,670,419, 4,540,602; and 4,486,435. Bloch and  
15 Speison (1983) Pharm. Acta Helv 58:14-22 teaches spray drying of hydrochlorothiazide and chlorthalidone (lipophilic drugs) and a hydrophilic adjuvant (pentaerythritol) in azeotropic solvents of dioxane-water and 2-ethoxyethanol-water. A number of Japanese Patent application Abstracts relate to spray drying of hydrophilic-hydrophobic product combinations, including JP 806766; JP 7242568; JP 7101884; JP 7101883; JP 71018982; JP  
20 7101881; and JP 4036233. Other foreign patent publications relevant to spray drying hydrophilic-hydrophobic product combinations include FR 2594693; DE 2209477; and WO 88/07870.

#### LYOPHILIZATION.

25 An iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) preparation can be made by lyophilization. Lyophilization is a freeze-drying process in which water is sublimed from the composition after it is frozen. The  
30 particular advantage associated with the lyophilization process is that biologicals and pharmaceuticals that are relatively unstable in an aqueous solution can be dried without



elevated temperatures (thereby eliminating the adverse thermal effects), and then stored in a dry state where there are few stability problems. With respect to the instant invention such techniques are particularly compatible with the incorporation of nucleic acids in perforated microstructures without compromising physiological activity. Methods for providing  
5 lyophilized particulates are known to those of skill in the art and it would clearly not require undue experimentation to provide dispersion compatible microstructures in accordance with the teachings herein. Accordingly, to the extent that lyophilization processes may be used to provide microstructures having the desired porosity and size, they are conformance with the teachings herein and are expressly contemplated as being within the scope of the instant  
10 invention.

### Targeting

For ease of exposition the formulations, compositions and methods in this section are discussed largely with regard to unmodified iRNAs. It should be understood, however, that these formulations, compositions and methods can be practiced with other iRNA agents, *e.g.*,  
15 modified iRNA agents, and such practice is within the invention.

In some embodiments, an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) is targeted to a particular cell. For example, a liposome  
20 or particle or other structure that includes a iRNA can also include a targeting moiety that recognizes a specific molecule on a target cell. The targeting moiety can be a molecule with a specific affinity for a target cell. Targeting moieties can include antibodies directed against a protein found on the surface of a target cell, or the ligand or a receptor-binding portion of a ligand for a molecule found on the surface of a target cell. For example, the targeting moiety  
25 can recognize a cancer-specific antigen (*e.g.*, CA15-3, CA19-9, CEA, or HER2/neu.) or a viral antigen, thus delivering the iRNA to a cancer cell or a virus-infected cell. Exemplary targeting moieties include antibodies (such as IgM, IgG, IgA, IgD, and the like, or a functional portions thereof), ligands for cell surface receptors (*e.g.*, ectodomains thereof).



Table 3 provides a number of antigens which can be used to target selected cells.

Table 3.

ANTIGEN	Exemplary tumor tissue
CEA (carcinoembryonic antigen)	colon, breast, lung
PSA (prostate specific antigen)	prostate cancer
CA-125	ovarian cancer
CA 15-3	breast cancer
CA 19-9	breast cancer
HER2/neu	breast cancer
$\alpha$ -feto protein	testicular cancer, hepatic cancer
$\beta$ -HCG (human chorionic gonadotropin)	testicular cancer, choriocarcinoma
MUC-1	breast cancer
Estrogen receptor	breast cancer, uterine cancer
Progesterone receptor	breast cancer, uterine cancer
EGFr (epidermal growth factor receptor)	bladder cancer

5

In one embodiment, the targeting moiety is attached to a liposome. For example, US 6,245,427 describes a method for targeting a liposome using a protein or peptide. In another example, a cationic lipid component of the liposome is derivatized with a targeting moiety. For example, WO 96/37194 describes converting N-glutaryl dioleoylphosphatidyl ethanolamine to a N-hydroxysuccinimide activated ester. The product was then coupled to an RGD peptide.

10

#### GENES AND DISEASES

In one aspect, the invention features, a method of treating a subject at risk for or afflicted with unwanted cell proliferation, *e.g.*, malignant or nonmalignant cell proliferation.

15 The method includes:

providing an iRNA agent, *e.g.*, an sRNA or iRNA agent described herein, *e.g.*, an iRNA having a structure described herein, where the iRNA is homologous to and can silence, *e.g.*, by cleavage, a gene which promotes unwanted cell proliferation;

administering an iRNA agent, *e.g.*, an sRNA or iRNA agent described herein to a subject, preferably a human subject, thereby treating the subject.

20

In a preferred embodiment the gene is a growth factor or growth factor receptor gene, a kinase, *e.g.*, a protein tyrosine, serine or threonine kinase gene, an adaptor protein gene, a gene encoding a G protein superfamily molecule, or a gene encoding a transcription factor.

5 In a preferred embodiment the iRNA agent silences the PDGF beta gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted PDGF beta expression, *e.g.*, testicular and lung cancers.

In another preferred embodiment the iRNA agent silences the Erb-B gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted Erb-B expression, *e.g.*, breast cancer.

10 In a preferred embodiment the iRNA agent silences the Src gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted Src expression, *e.g.*, colon cancers.

In a preferred embodiment the iRNA agent silences the CRK gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted CRK  
15 expression, *e.g.*, colon and lung cancers.

In a preferred embodiment the iRNA agent silences the GRB2 gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted GRB2 expression, *e.g.*, squamous cell carcinoma.

20 In another preferred embodiment the iRNA agent silences the RAS gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted RAS expression, *e.g.*, pancreatic, colon and lung cancers, and chronic leukemia.

In another preferred embodiment the iRNA agent silences the MEKK gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted MEKK expression, *e.g.*, squamous cell carcinoma, melanoma or leukemia.

25 In another preferred embodiment the iRNA agent silences the JNK gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted JNK expression, *e.g.*, pancreatic or breast cancers.

In a preferred embodiment the iRNA agent silences the RAF gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted RAF  
30 expression, *e.g.*, lung cancer or leukemia.

In a preferred embodiment the iRNA agent silences the Erk1/2 gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted Erk1/2 expression, *e.g.*, lung cancer.

5 In another preferred embodiment the iRNA agent silences the PCNA(p21) gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted PCNA expression, *e.g.*, lung cancer.

In a preferred embodiment the iRNA agent silences the MYB gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted MYB expression, *e.g.*, colon cancer or chronic myelogenous leukemia.

10 In a preferred embodiment the iRNA agent silences the c-MYC gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted c-MYC expression, *e.g.*, Burkitt's lymphoma or neuroblastoma.

In another preferred embodiment the iRNA agent silences the JUN gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted JUN  
15 expression, *e.g.*, ovarian, prostate or breast cancers.

In another preferred embodiment the iRNA agent silences the FOS gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted FOS expression, *e.g.*, skin or prostate cancers.

In a preferred embodiment the iRNA agent silences the BCL-2 gene, and thus can be  
20 used to treat a subject having or at risk for a disorder characterized by unwanted BCL-2 expression, *e.g.*, lung or prostate cancers or Non-Hodgkin lymphoma.

In a preferred embodiment the iRNA agent silences the Cyclin D gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted Cyclin D expression, *e.g.*, esophageal and colon cancers.

25 In a preferred embodiment the iRNA agent silences the VEGF gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted VEGF expression, *e.g.*, esophageal and colon cancers.

In a preferred embodiment the iRNA agent silences the EGFR gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted EGFR  
30 expression, *e.g.*, breast cancer.

In another preferred embodiment the iRNA agent silences the Cyclin A gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted Cyclin A expression, *e.g.*, lung and cervical cancers.

5 In another preferred embodiment the iRNA agent silences the Cyclin E gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted Cyclin E expression, *e.g.*, lung and breast cancers.

In another preferred embodiment the iRNA agent silences the WNT-1 gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted WNT-1 expression, *e.g.*, basal cell carcinoma.

10 In another preferred embodiment the iRNA agent silences the beta-catenin gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted beta-catenin expression, *e.g.*, adenocarcinoma or hepatocellular carcinoma.

In another preferred embodiment the iRNA agent silences the c-MET gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted c-MET expression, *e.g.*, hepatocellular carcinoma.

15 In another preferred embodiment the iRNA agent silences the PKC gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted PKC expression, *e.g.*, breast cancer.

20 In a preferred embodiment the iRNA agent silences the NFkB gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted NFkB expression, *e.g.*, breast cancer.

In a preferred embodiment the iRNA agent silences the STAT3 gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted STAT3 expression, *e.g.*, prostate cancer.

25 In another preferred embodiment the iRNA agent silences the survivin gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted survivin expression, *e.g.*, cervical or pancreatic cancers.

In another preferred embodiment the iRNA agent silences the Her2/Neu gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted Her2/Neu expression, *e.g.*, breast cancer.

In another preferred embodiment the iRNA agent silences the topoisomerase I gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted topoisomerase I expression, *e.g.*, ovarian and colon cancers.

5 In a preferred embodiment the iRNA agent silences the topoisomerase II alpha gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted topoisomerase II expression, *e.g.*, breast and colon cancers.

In a preferred embodiment the iRNA agent silences mutations in the p73 gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted p73 expression, *e.g.*, colorectal adenocarcinoma.

10 In a preferred embodiment the iRNA agent silences mutations in the p21(WAF1/CIP1) gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted p21(WAF1/CIP1) expression, *e.g.*, liver cancer.

In a preferred embodiment the iRNA agent silences mutations in the p27(KIP1) gene, and thus can be used to treat a subject having or at risk for a disorder characterized by  
15 unwanted p27(KIP1) expression, *e.g.*, liver cancer.

In a preferred embodiment the iRNA agent silences mutations in the PPM1D gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted PPM1D expression, *e.g.*, breast cancer.

20 In a preferred embodiment the iRNA agent silences mutations in the RAS gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted RAS expression, *e.g.*, breast cancer.

In another preferred embodiment the iRNA agent silences mutations in the caveolin I gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted caveolin I expression, *e.g.*, esophageal squamous cell carcinoma.

25 In another preferred embodiment the iRNA agent silences mutations in the MIB I gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted MIB I expression, *e.g.*, male breast carcinoma (MBC).

In another preferred embodiment the iRNA agent silences mutations in the MTAI gene, and thus can be used to treat a subject having or at risk for a disorder characterized by  
30 unwanted MTAI expression, *e.g.*, ovarian carcinoma.



In another preferred embodiment the iRNA agent silences mutations in the M68 gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted M68 expression, *e.g.*, human adenocarcinomas of the esophagus, stomach, colon, and rectum.

5 In preferred embodiments the iRNA agent silences mutations in tumor suppressor genes, and thus can be used as a method to promote apoptotic activity in combination with chemotherapeutics.

In a preferred embodiment the iRNA agent silences mutations in the p53 tumor suppressor gene, and thus can be used to treat a subject having or at risk for a disorder  
10 characterized by unwanted p53 expression, *e.g.*, gall bladder, pancreatic and lung cancers.

In a preferred embodiment the iRNA agent silences mutations in the p53 family member DN-p63, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted DN-p63 expression, *e.g.*, squamous cell carcinoma

In a preferred embodiment the iRNA agent silences mutations in the pRb tumor  
15 suppressor gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted pRb expression, *e.g.*, oral squamous cell carcinoma

In a preferred embodiment the iRNA agent silences mutations in the APC1 tumor suppressor gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted APC1 expression, *e.g.*, colon cancer.

20 In a preferred embodiment the iRNA agent silences mutations in the BRCA1 tumor suppressor gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted BRCA1 expression, *e.g.*, breast cancer.

In a preferred embodiment the iRNA agent silences mutations in the PTEN tumor suppressor gene, and thus can be used to treat a subject having or at risk for a disorder  
25 characterized by unwanted PTEN expression, *e.g.*, hamartomas, gliomas, and prostate and endometrial cancers.

In a preferred embodiment the iRNA agent silences MLL fusion genes, *e.g.*, MLL-AF9, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted MLL fusion gene expression, *e.g.*, acute leukemias.

In another preferred embodiment the iRNA agent silences the BCR/ABL fusion gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted BCR/ABL fusion gene expression, *e.g.*, acute and chronic leukemias.

5 In another preferred embodiment the iRNA agent silences the TEL/AML1 fusion gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted TEL/AML1 fusion gene expression, *e.g.*, childhood acute leukemia.

In another preferred embodiment the iRNA agent silences the EWS/FLI1 fusion gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted EWS/FLI1 fusion gene expression, *e.g.*, Ewing Sarcoma.

10 In another preferred embodiment the iRNA agent silences the TLS/FUS1 fusion gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted TLS/FUS1 fusion gene expression, *e.g.*, Myxoid liposarcoma.

In another preferred embodiment the iRNA agent silences the PAX3/FKHR fusion gene, and thus can be used to treat a subject having or at risk for a disorder characterized by  
15 unwanted PAX3/FKHR fusion gene expression, *e.g.*, Myxoid liposarcoma.

In another preferred embodiment the iRNA agent silences the AML1/ETO fusion gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted AML1/ETO fusion gene expression, *e.g.*, acute leukemia.

20 In another aspect, the invention features, a method of treating a subject, *e.g.*, a human, at risk for or afflicted with a disease or disorder that may benefit by angiogenesis inhibition *e.g.*, cancer. The method includes:

providing an iRNA agent, *e.g.*, an iRNA agent having a structure described herein, which iRNA agent is homologous to and can silence, *e.g.*, by cleavage, a gene which mediates angiogenesis;

25 administering the iRNA agent to a subject,  
thereby treating the subject.

In a preferred embodiment the iRNA agent silences the alpha v-integrin gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted alpha V integrin, *e.g.*, brain tumors or tumors of epithelial origin.

In a preferred embodiment the iRNA agent silences the Flt-1 receptor gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted Flt-1 receptors, eg. Cancer and rheumatoid arthritis.

5 In a preferred embodiment the iRNA agent silences the tubulin gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted tubulin, eg. Cancer and retinal neovascularization.

In a preferred embodiment the iRNA agent silences the tubulin gene, and thus can be used to treat a subject having or at risk for a disorder characterized by unwanted tubulin, eg. Cancer and retinal neovascularization.

10 In another aspect, the invention features a method of treating a subject infected with a virus or at risk for or afflicted with a disorder or disease associated with a viral infection. The method includes:

providing an iRNA agent, *e.g.*, and iRNA agent having a structure described herein, which iRNA agent is homologous to and can silence, *e.g.*, by cleavage, a viral gene of a  
15 cellular gene which mediates viral function, *e.g.*, entry or growth;  
administering the iRNA agent to a subject, preferably a human subject,  
thereby treating the subject.

Thus, the invention provides for a method of treating patients infected by the Human Papilloma Virus (HPV) or at risk for or afflicted with a disorder mediated by HPV, *e.g.*,  
20 cervical cancer. HPV is linked to 95% of cervical carcinomas and thus an antiviral therapy is an attractive method to treat these cancers and other symptoms of viral infection.

In a preferred embodiment, the expression of a HPV gene is reduced. In another preferred embodiment, the HPV gene is one of the group of E2, E6, or E7.

In a preferred embodiment the expression of a human gene that is required for HPV  
25 replication is reduced.

The invention also includes a method of treating patients infected by the Human Immunodeficiency Virus (HIV) or at risk for or afflicted with a disorder mediated by HIV, *e.g.*, Acquired Immune Deficiency Syndrome (AIDS).

In a preferred embodiment, the expression of a HIV gene is reduced. In another  
30 preferred embodiment, the HIV gene is CCR5, Gag, or Rev.

In a preferred embodiment the expression of a human gene that is required for HIV replication is reduced. In another preferred embodiment, the gene is CD4 or Tsg101.

The invention also includes a method for treating patients infected by the Hepatitis B Virus (HBV) or at risk for or afflicted with a disorder mediated by HBV, *e.g.*, cirrhosis and  
5 hepatocellular carcinoma.

In a preferred embodiment, the expression of a HBV gene is reduced. In another preferred embodiment, the targeted HBV gene encodes one of the group of the tail region of the HBV core protein, the pre-c region, or the c region. In another preferred embodiment, a targeted HBV-RNA sequence is comprised of the poly(A) tail.

10 In preferred embodiment the expression of a human gene that is required for HBV replication is reduced.

The invention also provides for a method of treating patients infected by the Hepatitis A Virus (HAV), or at risk for or afflicted with a disorder mediated by HAV.

In a preferred embodiment the expression of a human gene that is required for HAV  
15 replication is reduced.

The present invention provides for a method of treating patients infected by the Hepatitis C Virus (HCV), or at risk for or afflicted with a disorder mediated by HCV, *e.g.*, cirrhosis

In a preferred embodiment, the expression of a HCV gene is reduced.

20 In another preferred embodiment the expression of a human gene that is required for HCV replication is reduced.

The present invention also provides for a method of treating patients infected by the any of the group of Hepatitis Viral strains comprising hepatitis D, E, F, G, or H, or patients at risk for or afflicted with a disorder mediated by any of these strains of hepatitis.

25 In a preferred embodiment, the expression of a Hepatitis, D, E, F, G, or H gene is reduced.

In another preferred embodiment the expression of a human gene that is required for hepatitis D, E, F, G or H replication is reduced.

30 Methods of the invention also provide for treating patients infected by the Respiratory Syncytial Virus (RSV) or at risk for or afflicted with a disorder mediated by

RSV, *e.g.*, lower respiratory tract infection in infants and childhood asthma, pneumonia and other complications, *e.g.*, in the elderly.

In a preferred embodiment, the expression of a RSV gene is reduced. In another preferred embodiment, the targeted HBV gene encodes one of the group of genes N, L, or P.

5 In a preferred embodiment the expression of a human gene that is required for RSV replication is reduced.

Methods of the invention provide for treating patients infected by the Herpes Simplex Virus (HSV) or at risk for or afflicted with a disorder mediated by HSV, *e.g.*, genital herpes and cold sores as well as life-threatening or sight-impairing disease mainly in  
10 immunocompromised patients.

In a preferred embodiment, the expression of a HSV gene is reduced. In another preferred embodiment, the targeted HSV gene encodes DNA polymerase or the helicase-primase.

In a preferred embodiment the expression of a human gene that is required for HSV  
15 replication is reduced.

The invention also provides a method for treating patients infected by the herpes Cytomegalovirus (CMV) or at risk for or afflicted with a disorder mediated by CMV, *e.g.*, congenital virus infections and morbidity in immunocompromised patients.

In a preferred embodiment, the expression of a CMV gene is reduced.

20 In a preferred embodiment the expression of a human gene that is required for CMV replication is reduced.

Methods of the invention also provide for a method of treating patients infected by the herpes Epstein Barr Virus (EBV) or at risk for or afflicted with a disorder mediated by EBV, *e.g.*, NK/T-cell lymphoma, non-Hodgkin lymphoma, and Hodgkin disease.

25 In a preferred embodiment, the expression of a EBV gene is reduced.

In a preferred embodiment the expression of a human gene that is required for EBV replication is reduced.

Methods of the invention also provide for treating patients infected by Kaposi's Sarcoma-associated Herpes Virus (KSHV), also called human herpesvirus 8, or patients at  
30 risk for or afflicted with a disorder mediated by KSHV, *e.g.*, Kaposi's sarcoma, multicentric Castleman's disease and AIDS-associated primary effusion lymphoma.



In a preferred embodiment, the expression of a KSHV gene is reduced.

In a preferred embodiment the expression of a human gene that is required for KSHV replication is reduced.

The invention also includes a method for treating patients infected by the JC Virus (JCV) or a disease or disorder associated with this virus, *e.g.*, progressive multifocal leukoencephalopathy (PML).

In a preferred embodiment, the expression of a JCV gene is reduced.

In preferred embodiment the expression of a human gene that is required for JCV replication is reduced.

Methods of the invention also provide for treating patients infected by the myxovirus or at risk for or afflicted with a disorder mediated by myxovirus, *e.g.*, influenza.

In a preferred embodiment, the expression of a myxovirus gene is reduced.

In a preferred embodiment the expression of a human gene that is required for myxovirus replication is reduced.

Methods of the invention also provide for treating patients infected by the rhinovirus or at risk for or afflicted with a disorder mediated by rhinovirus, *e.g.*, the common cold.

In a preferred embodiment, the expression of a rhinovirus gene is reduced.

In preferred embodiment the expression of a human gene that is required for rhinovirus replication is reduced.

Methods of the invention also provide for treating patients infected by the coronavirus or at risk for or afflicted with a disorder mediated by coronavirus, *e.g.*, the common cold.

In a preferred embodiment, the expression of a coronavirus gene is reduced.

In preferred embodiment the expression of a human gene that is required for coronavirus replication is reduced.

Methods of the invention also provide for treating patients infected by the flavivirus West Nile or at risk for or afflicted with a disorder mediated by West Nile Virus.

In a preferred embodiment, the expression of a West Nile Virus gene is reduced. In another preferred embodiment, the West Nile Virus gene is one of the group comprising E, NS3, or NS5.

In a preferred embodiment the expression of a human gene that is required for West Nile Virus replication is reduced.

Methods of the invention also provide for treating patients infected by the St. Louis Encephalitis flavivirus, or at risk for or afflicted with a disease or disorder associated with this virus, *e.g.*, viral haemorrhagic fever or neurological disease.

In a preferred embodiment, the expression of a St. Louis Encephalitis gene is reduced.

5 In a preferred embodiment the expression of a human gene that is required for St. Louis Encephalitis virus replication is reduced.

Methods of the invention also provide for treating patients infected by the Tick-borne encephalitis flavivirus, or at risk for or afflicted with a disorder mediated by Tick-borne encephalitis virus, *e.g.*, viral haemorrhagic fever and neurological disease.

10 In a preferred embodiment, the expression of a Tick-borne encephalitis virus gene is reduced.

In a preferred embodiment the expression of a human gene that is required for Tick-borne encephalitis virus replication is reduced.

15 Methods of the invention also provide for methods of treating patients infected by the Murray Valley encephalitis flavivirus, which commonly results in viral haemorrhagic fever and neurological disease.

In a preferred embodiment, the expression of a Murray Valley encephalitis virus gene is reduced.

20 In a preferred embodiment the expression of a human gene that is required for Murray Valley encephalitis virus replication is reduced.

The invention also includes methods for treating patients infected by the dengue flavivirus, or a disease or disorder associated with this virus, *e.g.*, dengue haemorrhagic fever.

In a preferred embodiment, the expression of a dengue virus gene is reduced.

25 In a preferred embodiment the expression of a human gene that is required for dengue virus replication is reduced.

Methods of the invention also provide for treating patients infected by the Simian Virus 40 (SV40) or at risk for or afflicted with a disorder mediated by SV40, *e.g.*, tumorigenesis.

30 In a preferred embodiment, the expression of a SV40 gene is reduced.

In a preferred embodiment the expression of a human gene that is required for SV40 replication is reduced.

The invention also includes methods for treating patients infected by the Human T Cell Lymphotropic Virus (HTLV), or a disease or disorder associated with this virus, *e.g.*,  
5 leukemia and myelopathy.

In a preferred embodiment, the expression of a HTLV gene is reduced. In another preferred embodiment the HTLV1 gene is the Tax transcriptional activator.

In a preferred embodiment the expression of a human gene that is required for HTLV replication is reduced.

10 Methods of the invention also provide for treating patients infected by the Moloney-Murine Leukemia Virus (Mo-MuLV) or at risk for or afflicted with a disorder mediated by Mo-MuLV, *e.g.*, T-cell leukemia.

In a preferred embodiment, the expression of a Mo-MuLV gene is reduced.

In a preferred embodiment the expression of a human gene that is required for Mo-  
15 MuLV replication is reduced.

Methods of the invention also provide for treating patients infected by the encephalomyocarditis virus (EMCV) or at risk for or afflicted with a disorder mediated by EMCV, *e.g.* myocarditis. EMCV leads to myocarditis in mice and pigs and is capable of infecting human myocardial cells. This virus is therefore a concern for patients undergoing  
20 xenotransplantation.

In a preferred embodiment, the expression of a EMCV gene is reduced.

In a preferred embodiment the expression of a human gene that is required for EMCV replication is reduced.

The invention also includes a method for treating patients infected by the measles  
25 virus (MV) or at risk for or afflicted with a disorder mediated by MV, *e.g.* measles.

In a preferred embodiment, the expression of a MV gene is reduced.

In a preferred embodiment the expression of a human gene that is required for MV replication is reduced.

The invention also includes a method for treating patients infected by the Varicella  
30 zoster virus (VZV) or at risk for or afflicted with a disorder mediated by VZV, *e.g.* chicken pox or shingles (also called zoster).

In a preferred embodiment, the expression of a VZV gene is reduced.

In a preferred embodiment the expression of a human gene that is required for VZV replication is reduced.

5 The invention also includes a method for treating patients infected by an adenovirus or at risk for or afflicted with a disorder mediated by an adenovirus, *e.g.* respiratory tract infection.

In a preferred embodiment, the expression of an adenovirus gene is reduced.

In a preferred embodiment the expression of a human gene that is required for adenovirus replication is reduced.

10 The invention includes a method for treating patients infected by a yellow fever virus (YFV) or at risk for or afflicted with a disorder mediated by a YFV, *e.g.* respiratory tract infection.

In a preferred embodiment, the expression of a YFV gene is reduced. In another preferred embodiment, the preferred gene is one of a group that includes the E, NS2A, or  
15 NS3 genes.

In a preferred embodiment the expression of a human gene that is required for YFV replication is reduced.

Methods of the invention also provide for treating patients infected by the poliovirus or at risk for or afflicted with a disorder mediated by poliovirus, *e.g.*, polio.

20 In a preferred embodiment, the expression of a poliovirus gene is reduced.

In a preferred embodiment the expression of a human gene that is required for poliovirus replication is reduced.

Methods of the invention also provide for treating patients infected by a poxvirus or at risk for or afflicted with a disorder mediated by a poxvirus, *e.g.*, smallpox

25 In a preferred embodiment, the expression of a poxvirus gene is reduced.

In a preferred embodiment the expression of a human gene that is required for poxvirus replication is reduced.

In another, aspect the invention features methods of treating a subject infected with a pathogen, *e.g.*, a bacterial, amoebic, parasitic, or fungal pathogen. The method includes:

30 providing a iRNA agent, *e.g.*, a siRNA having a structure described herein, where siRNA is homologous to and can silence, *e.g.*, by cleavage of a pathogen gene;

administering the iRNA agent to a subject, preferably a human subject, thereby treating the subject.

The target gene can be one involved in growth, cell wall synthesis, protein synthesis, transcription, energy metabolism, *e.g.*, the Krebs cycle, or toxin production.

5        Thus, the present invention provides for a method of treating patients infected by a plasmodium that causes malaria.

In a preferred embodiment, the expression of a plasmodium gene is reduced. In another preferred embodiment, the gene is apical membrane antigen 1 (AMA1).

10       In a preferred embodiment the expression of a human gene that is required for plasmodium replication is reduced.

The invention also includes methods for treating patients infected by the *Mycobacterium ulcerans*, or a disease or disorder associated with this pathogen, *e.g.* Buruli ulcers.

15       In a preferred embodiment, the expression of a *Mycobacterium ulcerans* gene is reduced.

In a preferred embodiment the expression of a human gene that is required for *Mycobacterium ulcerans* replication is reduced.

20       The invention also includes methods for treating patients infected by the *Mycobacterium tuberculosis*, or a disease or disorder associated with this pathogen, *e.g.* tuberculosis.

In a preferred embodiment, the expression of a *Mycobacterium tuberculosis* gene is reduced.

In a preferred embodiment the expression of a human gene that is required for *Mycobacterium tuberculosis* replication is reduced.

25       The invention also includes methods for treating patients infected by the *Mycobacterium leprae*, or a disease or disorder associated with this pathogen, *e.g.* leprosy.

In a preferred embodiment, the expression of a *Mycobacterium leprae* gene is reduced.

30       In a preferred embodiment the expression of a human gene that is required for *Mycobacterium leprae* replication is reduced.



The invention also includes methods for treating patients infected by the bacteria *Staphylococcus aureus*, or a disease or disorder associated with this pathogen, *e.g.* infections of the skin and mucous membranes.

5 In a preferred embodiment, the expression of a *Staphylococcus aureus* gene is reduced.

In a preferred embodiment the expression of a human gene that is required for *Staphylococcus aureus* replication is reduced.

The invention also includes methods for treating patients infected by the bacteria *Streptococcus pneumoniae*, or a disease or disorder associated with this pathogen, *e.g.* pneumonia or childhood lower respiratory tract infection.

In a preferred embodiment, the expression of a *Streptococcus pneumoniae* gene is reduced.

In a preferred embodiment the expression of a human gene that is required for *Streptococcus pneumoniae* replication is reduced.

15 The invention also includes methods for treating patients infected by the bacteria *Streptococcus pyogenes*, or a disease or disorder associated with this pathogen, *e.g.* Strep throat or Scarlet fever.

In a preferred embodiment, the expression of a *Streptococcus pyogenes* gene is reduced.

20 In a preferred embodiment the expression of a human gene that is required for *Streptococcus pyogenes* replication is reduced.

The invention also includes methods for treating patients infected by the bacteria *Chlamydia pneumoniae*, or a disease or disorder associated with this pathogen, *e.g.* pneumonia or childhood lower respiratory tract infection

25 In a preferred embodiment, the expression of a *Chlamydia pneumoniae* gene is reduced.

In a preferred embodiment the expression of a human gene that is required for *Chlamydia pneumoniae* replication is reduced.

The invention also includes methods for treating patients infected by the bacteria *Mycoplasma pneumoniae*, or a disease or disorder associated with this pathogen, *e.g.* pneumonia or childhood lower respiratory tract infection

In a preferred embodiment, the expression of a *Mycoplasma pneumoniae* gene is reduced.

In a preferred embodiment the expression of a human gene that is required for *Mycoplasma pneumoniae* replication is reduced.

5 In one aspect, the invention features, a method of treating a subject, *e.g.*, a human, at risk for or afflicted with a disease or disorder characterized by an unwanted immune response, *e.g.*, an inflammatory disease or disorder, or an autoimmune disease or disorder. The method includes:

10 providing an iRNA agent, *e.g.*, an iRNA agent having a structure described herein, which iRNA agent is homologous to and can silence, *e.g.*, by cleavage, a gene which mediates an unwanted immune response;  
administering the iRNA agent to a subject,  
thereby treating the subject.

15 In a preferred embodiment the disease or disorder is an ischemia or reperfusion injury, *e.g.*, ischemia or reperfusion injury associated with acute myocardial infarction, unstable angina, cardiopulmonary bypass, surgical intervention *e.g.*, angioplasty, *e.g.*, percutaneous transluminal coronary angioplasty, the response to a transplanted organ or tissue, *e.g.*, transplanted cardiac or vascular tissue; or thrombolysis.

20 In a preferred embodiment the disease or disorder is restenosis, *e.g.*, restenosis associated with surgical intervention *e.g.*, angioplasty, *e.g.*, percutaneous transluminal coronary angioplasty.

In a preferred embodiment the disease or disorder is Inflammatory Bowel Disease, *e.g.*, Crohn Disease or Ulcerative Colitis.

25 In a preferred embodiment the disease or disorder is inflammation associated with an infection or injury.

In a preferred embodiment the disease or disorder is asthma, lupus, multiple sclerosis, diabetes, *e.g.*, type II diabetes, arthritis, *e.g.*, rheumatoid or psoriatic.

In particularly preferred embodiments the iRNA agent silences an integrin or co-ligand thereof, *e.g.*, VLA4, VCAM, ICAM.

30 In particularly preferred embodiments the iRNA agent silences a selectin or co-ligand thereof, *e.g.*, P-selectin, E-selectin (ELAM), I-selectin, P-selectin glycoprotein-1 (PSGL-1).

In particularly preferred embodiments the iRNA agent silences a component of the complement system, *e.g.*, C3, C5, C3aR, C5aR, C3 convertase, C5 convertase.

In particularly preferred embodiments the iRNA agent silences a chemokine or receptor thereof, *e.g.*, TNFI, TNFJ, IL-1I, IL-1J, IL -2, IL-2R, IL-4, IL-4R, IL-5, IL-6, IL-8,  
5 TNFRI, TNFRII, IgE, SCYA11, CCR3.

In other embodiments the iRNA agent silences GCSF, Gro1, Gro2, Gro3, PF4, MIG, Pro-Platelet Basic Protein (PPBP), MIP-1I, MIP-1J, RANTES, MCP-1, MCP-2, MCP-3, CMBKR1, CMBKR2, CMBKR3, CMBKR5, AIF-1, I-309.

In one aspect, the invention features, a method of treating a subject, *e.g.*, a human, at  
10 risk for or afflicted with acute pain or chronic pain. The method includes:

providing an iRNA agent, which iRNA is homologous to and can silence, *e.g.*, by cleavage, a gene which mediates the processing of pain;  
administering the iRNA to a subject,  
thereby treating the subject.

15 In particularly preferred embodiments the iRNA agent silences a component of an ion channel.

In particularly preferred embodiments the iRNA agent silences a neurotransmitter receptor or ligand.

In one aspect, the invention features, a method of treating a subject, *e.g.*, a human, at  
20 risk for or afflicted with a neurological disease or disorder. The method includes:

providing an iRNA agent which iRNA is homologous to and can silence, *e.g.*, by cleavage, a gene which mediates a neurological disease or disorder;  
administering the to a subject,  
thereby treating the subject.

25 In a preferred embodiment the disease or disorder is Alzheimer Disease or Parkinson Disease.

In particularly preferred embodiments the iRNA agent silences an amyloid-family gene, *e.g.*, APP; a presenilin gene, *e.g.*, PSEN1 and PSEN2, or I-synuclein.

In a preferred embodiment the disease or disorder is a neurodegenerative trinucleotide  
30 repeat disorder, *e.g.*, Huntington disease, dentatorubral pallidolusian atrophy or a spinocerebellar ataxia, *e.g.*, SCA1, SCA2, SCA3 (Machado-Joseph disease), SCA7 or SCA8.

In particularly preferred embodiments the iRNA agent silences HD, DRPLA, SCA1, SCA2, MJD1, CACNL1A4, SCA7, SCA8.

The loss of heterozygosity (LOH) can result in hemizyosity for sequence, *e.g.*, genes, in the area of LOH. This can result in a significant genetic difference between normal and disease-state cells, *e.g.*, cancer cells, and provides a useful difference between normal and disease-state cells, *e.g.*, cancer cells. This difference can arise because a gene or other sequence is heterozygous in euploid cells but is hemizygous in cells having LOH. The regions of LOH will often include a gene, the loss of which promotes unwanted proliferation, *e.g.*, a tumor suppressor gene, and other sequences including, *e.g.*, other genes, in some cases a gene which is essential for normal function, *e.g.*, growth. Methods of the invention rely, in part, on the specific cleavage or silencing of one allele of an essential gene with an iRNA agent of the invention. The iRNA agent is selected such that it targets the single allele of the essential gene found in the cells having LOH but does not silence the other allele, which is present in cells which do not show LOH. In essence, it discriminates between the two alleles, preferentially silencing the selected allele. In essence polymorphisms, *e.g.*, SNPs of essential genes that are affected by LOH, are used as a target for a disorder characterized by cells having LOH, *e.g.*, cancer cells having LOH.

*E.g.*, one of ordinary skill in the art can identify essential genes which are in proximity to tumor suppressor genes, and which are within a LOH region which includes the tumor suppressor gene. The gene encoding the large subunit of human RNA polymerase II, POLR2A, a gene located in close proximity to the tumor suppressor gene p53, is such a gene. It frequently occurs within a region of LOH in cancer cells. Other genes that occur within LOH regions and are lost in many cancer cell types include the group comprising replication protein A 70-kDa subunit, replication protein A 32-kD, ribonucleotide reductase, thymidilate synthase, TATA associated factor 2H, ribosomal protein S14, eukaryotic initiation factor 5A, alanyl tRNA synthetase, cysteinyl tRNA synthetase, NaK ATPase, alpha-1 subunit, and transferrin receptor.

Accordingly, the invention features, a method of treating a disorder characterized by LOH, *e.g.*, cancer. The method includes:

optionally, determining the genotype of the allele of a gene in the region of LOH and preferably determining the genotype of both alleles of the gene in a normal cell;

providing an iRNA agent which preferentially cleaves or silences the allele found in the LOH cells;

administering the iRNA to the subject,  
thereby treating the disorder.

5 The invention also includes a iRNA agent disclosed herein, *e.g.*, an iRNA agent which can preferentially silence, *e.g.*, cleave, one allele of a polymorphic gene

In another aspect, the invention provides a method of cleaving or silencing more than one gene with an iRNA agent. In these embodiments the iRNA agent is selected so that it has sufficient homology to a sequence found in more than one gene. For example, the  
10 sequence AAGCTGGCCCTGGACATGGAGAT (SEQ ID NO:6736) is conserved between mouse lamin B1, lamin B2, keratin complex 2-gene 1 and lamin A/C. Thus an iRNA agent targeted to this sequence would effectively silence the entire collection of genes.

The invention also includes an iRNA agent disclosed herein, which can silence more than one gene.

#### 15 ROUTE OF DELIVERY

For ease of exposition the formulations, compositions and methods in this section are discussed largely with regard to unmodified iRNA agents. It should be understood, however, that these formulations, compositions and methods can be practiced with other iRNA agents, *e.g.*, modified iRNA agents, and such practice is within the invention. A composition that  
20 includes a iRNA can be delivered to a subject by a variety of routes. Exemplary routes include: intravenous, topical, rectal, anal, vaginal, nasal, pulmonary, ocular.

The iRNA molecules of the invention can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically include one or more species of iRNA and a pharmaceutically acceptable carrier. As used herein the language  
25 “pharmaceutically acceptable carrier” is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the



compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

The pharmaceutical compositions of the present invention may be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the  
5 area to be treated. Administration may be topical (including ophthalmic, vaginal, rectal, intranasal, transdermal), oral or parenteral. Parenteral administration includes intravenous drip, subcutaneous, intraperitoneal or intramuscular injection, or intrathecal or intraventricular administration.

The route and site of administration may be chosen to enhance targeting. For  
10 example, to target muscle cells, intramuscular injection into the muscles of interest would be a logical choice. Lung cells might be targeted by administering the iRNA in aerosol form. The vascular endothelial cells could be targeted by coating a balloon catheter with the iRNA and mechanically introducing the DNA.

Formulations for topical administration may include transdermal patches, ointments,  
15 lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful.

Compositions for oral administration include powders or granules, suspensions or solutions in water, syrups, elixirs or non-aqueous media, tablets, capsules, lozenges, or  
20 troches. In the case of tablets, carriers that can be used include lactose, sodium citrate and salts of phosphoric acid. Various disintegrants such as starch, and lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc, are commonly used in tablets. For oral administration in capsule form, useful diluents are lactose and high molecular weight polyethylene glycols. When aqueous suspensions are required for oral use, the nucleic acid  
25 compositions can be combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents can be added.

Compositions for intrathecal or intraventricular administration may include sterile aqueous solutions which may also contain buffers, diluents and other suitable additives.

Formulations for parenteral administration may include sterile aqueous solutions  
30 which may also contain buffers, diluents and other suitable additives. Intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a

reservoir. For intravenous use, the total concentration of solutes should be controlled to render the preparation isotonic.

For ocular administration, ointments or droppable liquids may be delivered by ocular delivery systems known to the art such as applicators or eye droppers. Such compositions can  
5 include mucomimetics such as hyaluronic acid, chondroitin sulfate, hydroxypropyl methylcellulose or poly(vinyl alcohol), preservatives such as sorbic acid, EDTA or benzylchromium chloride, and the usual quantities of diluents and/or carriers.

#### Topical Delivery

For ease of exposition the formulations, compositions and methods in this section are  
10 discussed largely with regard to unmodified iRNA agents. It should be understood, however, that these formulations, compositions and methods can be practiced with other iRNA agents, *e.g.*, modified iRNA agents, and such practice is within the invention. In a preferred embodiment, an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA  
15 which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) is delivered to a subject via topical administration. "Topical administration" refers to the delivery to a subject by contacting the formulation directly to a surface of the subject. The most common form of topical delivery is to the skin, but a composition disclosed herein can also be directly applied to other surfaces of the body, *e.g.*,  
20 to the eye, a mucous membrane, to surfaces of a body cavity or to an internal surface. As mentioned above, the most common topical delivery is to the skin. The term encompasses several routes of administration including, but not limited to, topical and transdermal. These modes of administration typically include penetration of the skin's permeability barrier and efficient delivery to the target tissue or stratum. Topical administration can be used as a  
25 means to penetrate the epidermis and dermis and ultimately achieve systemic delivery of the composition. Topical administration can also be used as a means to selectively deliver oligonucleotides to the epidermis or dermis of a subject, or to specific strata thereof, or to an underlying tissue.

The term "skin," as used herein, refers to the epidermis and/or dermis of an animal.  
30 Mammalian skin consists of two major, distinct layers. The outer layer of the skin is called the epidermis. The epidermis is comprised of the stratum corneum, the stratum granulosum,

the stratum spinosum, and the stratum basale, with the stratum corneum being at the surface of the skin and the stratum basale being the deepest portion of the epidermis. The epidermis is between 50  $\mu\text{m}$  and 0.2 mm thick, depending on its location on the body.

Beneath the epidermis is the dermis, which is significantly thicker than the epidermis.  
5 The dermis is primarily composed of collagen in the form of fibrous bundles. The collagenous bundles provide support for, inter alia, blood vessels, lymph capillaries, glands, nerve endings and immunologically active cells.

One of the major functions of the skin as an organ is to regulate the entry of substances into the body. The principal permeability barrier of the skin is provided by the  
10 stratum corneum, which is formed from many layers of cells in various states of differentiation. The spaces between cells in the stratum corneum is filled with different lipids arranged in lattice-like formations that provide seals to further enhance the skins permeability barrier.

The permeability barrier provided by the skin is such that it is largely impermeable to  
15 molecules having molecular weight greater than about 750 Da. For larger molecules to cross the skin's permeability barrier, mechanisms other than normal osmosis must be used.

Several factors determine the permeability of the skin to administered agents. These factors include the characteristics of the treated skin, the characteristics of the delivery agent, interactions between both the drug and delivery agent and the drug and skin, the dosage of  
20 the drug applied, the form of treatment, and the post treatment regimen. To selectively target the epidermis and dermis, it is sometimes possible to formulate a composition that comprises one or more penetration enhancers that will enable penetration of the drug to a preselected stratum.

Transdermal delivery is a valuable route for the administration of lipid soluble  
25 therapeutics. The dermis is more permeable than the epidermis and therefore absorption is much more rapid through abraded, burned or denuded skin. Inflammation and other physiologic conditions that increase blood flow to the skin also enhance transdermal adsorption. Absorption via this route may be enhanced by the use of an oily vehicle (inunction) or through the use of one or more penetration enhancers. Other effective ways to  
30 deliver a composition disclosed herein via the transdermal route include hydration of the skin and the use of controlled release topical patches. The transdermal route provides a

potentially effective means to deliver a composition disclosed herein for systemic and/or local therapy.

In addition, iontophoresis (transfer of ionic solutes through biological membranes under the influence of an electric field) (Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p. 163), phonophoresis or sonophoresis (use of ultrasound to enhance the absorption of various therapeutic agents across biological membranes, notably the skin and the cornea) (Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p. 166), and optimization of vehicle characteristics relative to dose position and retention at the site of administration (Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p. 168) may be useful methods for enhancing the transport of topically applied compositions across skin and mucosal sites.

The compositions and methods provided may also be used to examine the function of various proteins and genes *in vitro* in cultured or preserved dermal tissues and in animals. The invention can be thus applied to examine the function of any gene. The methods of the invention can also be used therapeutically or prophylactically. For example, for the treatment of animals that are known or suspected to suffer from diseases such as psoriasis, lichen planus, toxic epidermal necrolysis, erythema multiforme, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, Kaposi's sarcoma, pulmonary fibrosis, Lyme disease and viral, fungal and bacterial infections of the skin.

#### Pulmonary Delivery

For ease of exposition the formulations, compositions and methods in this section are discussed largely with regard to unmodified iRNA agents. It should be understood, however, that these formulations, compositions and methods can be practiced with other iRNA agents, *e.g.*, modified iRNA agents, and such practice is within the invention. A composition that includes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) can be administered to a subject by pulmonary delivery. Pulmonary delivery compositions can be delivered by inhalation by the patient of a dispersion so that the composition, preferably iRNA, within the dispersion can reach the lung where it can be



readily absorbed through the alveolar region directly into blood circulation. Pulmonary delivery can be effective both for systemic delivery and for localized delivery to treat diseases of the lungs.

Pulmonary delivery can be achieved by different approaches, including the use of nebulized, aerosolized, micellular and dry powder-based formulations. Delivery can be achieved with liquid nebulizers, aerosol-based inhalers, and dry powder dispersion devices. Metered-dose devices are preferred. One of the benefits of using an atomizer or inhaler is that the potential for contamination is minimized because the devices are self contained. Dry powder dispersion devices, for example, deliver drugs that may be readily formulated as dry powders. A iRNA composition may be stably stored as lyophilized or spray-dried powders by itself or in combination with suitable powder carriers. The delivery of a composition for inhalation can be mediated by a dosing timing element which can include a timer, a dose counter, time measuring device, or a time indicator which when incorporated into the device enables dose tracking, compliance monitoring, and/or dose triggering to a patient during administration of the aerosol medicament.

The term "powder" means a composition that consists of finely dispersed solid particles that are free flowing and capable of being readily dispersed in an inhalation device and subsequently inhaled by a subject so that the particles reach the lungs to permit penetration into the alveoli. Thus, the powder is said to be "respirable." Preferably the average particle size is less than about 10  $\mu\text{m}$  in diameter preferably with a relatively uniform spheroidal shape distribution. More preferably the diameter is less than about 7.5  $\mu\text{m}$  and most preferably less than about 5.0  $\mu\text{m}$ . Usually the particle size distribution is between about 0.1  $\mu\text{m}$  and about 5  $\mu\text{m}$  in diameter, particularly about 0.3  $\mu\text{m}$  to about 5  $\mu\text{m}$ .

The term "dry" means that the composition has a moisture content below about 10% by weight (% w) water, usually below about 5% w and preferably less it than about 3% w. A dry composition can be such that the particles are readily dispersible in an inhalation device to form an aerosol.

The term "therapeutically effective amount" is the amount present in the composition that is needed to provide the desired level of drug in the subject to be treated to give the anticipated physiological response.



The term “physiologically effective amount”<sup>5</sup> is that amount delivered to a subject to give the desired palliative or curative effect.

The term “pharmaceutically acceptable carrier” means that the carrier can be taken into the lungs with no significant adverse toxicological effects on the lungs.

5 The types of pharmaceutical excipients that are useful as carrier include stabilizers such as human serum albumin (HSA), bulking agents such as carbohydrates, amino acids and polypeptides; pH adjusters or buffers; salts such as sodium chloride; and the like. These carriers may be in a crystalline or amorphous form or may be a mixture of the two.

Bulking agents that are particularly valuable include compatible carbohydrates,  
10 polypeptides, amino acids or combinations thereof. Suitable carbohydrates include monosaccharides such as galactose, D-mannose, sorbose, and the like; disaccharides, such as lactose, trehalose, and the like; cyclodextrins, such as 2-hydroxypropyl-.beta.-cyclodextrin; and polysaccharides, such as raffinose, maltodextrins, dextrans, and the like; alditols, such as mannitol, xylitol, and the like. A preferred group of carbohydrates includes lactose,  
15 threhalose, raffinose maltodextrins, and mannitol. Suitable polypeptides include aspartame. Amino acids include alanine and glycine, with glycine being preferred.

Additives, which are minor components of the composition of this invention, may be included for conformational stability during spray drying and for improving dispersibility of the powder. These additives include hydrophobic amino acids such as tryptophan, tyrosine,  
20 leucine, phenylalanine, and the like.

Suitable pH adjusters or buffers include organic salts prepared from organic acids and bases, such as sodium citrate, sodium ascorbate, and the like; sodium citrate is preferred.

Pulmonary administration of a micellar iRNA formulation may be achieved through metered dose spray devices with propellants such as tetrafluoroethane, heptafluoroethane,  
25 dimethylfluoropropane, tetrafluoropropane, butane, isobutane, dimethyl ether and other non-CFC and CFC propellants.

#### Oral or Nasal Delivery

For ease of exposition the formulations, compositions and methods in this section are discussed largely with regard to unmodified iRNA agents. It should be understood, however,  
30 that these formulations, compositions and methods can be practiced with other iRNA agents, *e.g.*, modified iRNA agents, and such practice is within the invention. Both the oral and

nasal membranes offer advantages over other routes of administration. For example, drugs administered through these membranes have a rapid onset of action, provide therapeutic plasma levels, avoid first pass effect of hepatic metabolism, and avoid exposure of the drug to the hostile gastrointestinal (GI) environment. Additional advantages include easy access  
5 to the membrane sites so that the drug can be applied, localized and removed easily.

In oral delivery, compositions can be targeted to a surface of the oral cavity, *e.g.*, to sublingual mucosa which includes the membrane of ventral surface of the tongue and the floor of the mouth or the buccal mucosa which constitutes the lining of the cheek. The sublingual mucosa is relatively permeable thus giving rapid absorption and acceptable  
10 bioavailability of many drugs. Further, the sublingual mucosa is convenient, acceptable and easily accessible.

The ability of molecules to permeate through the oral mucosa appears to be related to molecular size, lipid solubility and peptide protein ionization. Small molecules, less than 1000 daltons appear to cross mucosa rapidly. As molecular size increases, the permeability  
15 decreases rapidly. Lipid soluble compounds are more permeable than non-lipid soluble molecules. Maximum absorption occurs when molecules are un-ionized or neutral in electrical charges. Therefore charged molecules present the biggest challenges to absorption through the oral mucosae.

A pharmaceutical composition of iRNA may also be administered to the buccal cavity  
20 of a human being by spraying into the cavity, without inhalation, from a metered dose spray dispenser, a mixed micellar pharmaceutical formulation as described above and a propellant. In one embodiment, the dispenser is first shaken prior to spraying the pharmaceutical formulation and propellant into the buccal cavity.

### Devices

25 For ease of exposition the devices, formulations, compositions and methods in this section are discussed largely with regard to unmodified iRNA agents. It should be understood, however, that these devices, formulations, compositions and methods can be practiced with other iRNA agents, *e.g.*, modified iRNA agents, and such practice is within the invention. An iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a  
30 precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or

precursor thereof) can be disposed on or in a device, *e.g.*, a device which implanted or otherwise placed in a subject. Exemplary devices include devices which are introduced into the vasculature, *e.g.*, devices inserted into the lumen of a vascular tissue, or which devices themselves form a part of the vasculature, including stents, catheters, heart valves, and other  
5 vascular devices. These devices, *e.g.*, catheters or stents, can be placed in the vasculature of the lung, heart, or leg.

Other devices include non-vascular devices, *e.g.*, devices implanted in the peritoneum, or in organ or glandular tissue, *e.g.*, artificial organs. The device can release a therapeutic substance in addition to a iRNA, *e.g.*, a device can release insulin.

10 Other devices include artificial joints, *e.g.*, hip joints, and other orthopedic implants.

In one embodiment, unit doses or measured doses of a composition that includes iRNA are dispensed by an implanted device. The device can include a sensor that monitors a parameter within a subject. For example, the device can include pump, *e.g.*, and, optionally, associated electronics.

15 Tissue, *e.g.*, cells or organs can be treated with An iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) *ex vivo* and then administered or implanted in a subject.

20 The tissue can be autologous, allogeneic, or xenogeneic tissue. *E.g.*, tissue can be treated to reduce graft v. host disease. In other embodiments, the tissue is allogeneic and the tissue is treated to treat a disorder characterized by unwanted gene expression in that tissue. *E.g.*, tissue, *e.g.*, hematopoietic cells, *e.g.*, bone marrow hematopoietic cells, can be treated to inhibit unwanted cell proliferation.

25 Introduction of treated tissue, whether autologous or transplant, can be combined with other therapies.

In some implementations, the iRNA treated cells are insulated from other cells, *e.g.*, by a semi-permeable porous barrier that prevents the cells from leaving the implant, but enables molecules from the body to reach the cells and molecules produced by the cells to  
30 enter the body. In one embodiment, the porous barrier is formed from alginate.

In one embodiment, a contraceptive device is coated with or contains an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof). Exemplary  
5 devices include condoms, diaphragms, IUD (implantable uterine devices, sponges, vaginal sheaths, and birth control devices. In one embodiment, the iRNA is chosen to inactive sperm or egg. In another embodiment, the iRNA is chosen to be complementary to a viral or pathogen RNA, *e.g.*, an RNA of an STD. In some instances, the iRNA composition can include a spermicide.

## 10 DOSAGE

In one aspect, the invention features a method of administering an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, to a subject (*e.g.*, a human subject). The method includes administering a unit dose of the iRNA agent, *e.g.*, a sRNA agent, *e.g.*, double stranded sRNA agent that (a) the double-stranded part is 19-25 nucleotides (nt) long,  
15 preferably 21-23 nt, (b) is complementary to a target RNA (*e.g.*, an endogenous or pathogen target RNA), and, optionally, (c) includes at least one 3' overhang 1-5 nucleotide long. In one embodiment, the unit dose is less than 1.4 mg per kg of bodyweight, or less than 10, 5, 2, 1, 0.5, 0.1, 0.05, 0.01, 0.005, 0.001, 0.0005, 0.0001, 0.00005 or 0.00001 mg per kg of bodyweight, and less than 200 nmole of RNA agent (*e.g.* about  $4.4 \times 10^{16}$  copies) per kg of  
20 bodyweight, or less than 1500, 750, 300, 150, 75, 15, 7.5, 1.5, 0.75, 0.15, 0.075, 0.015, 0.0075, 0.0015, 0.00075, 0.00015 nmole of RNA agent per kg of bodyweight.

The defined amount can be an amount effective to treat or prevent a disease or disorder, *e.g.*, a disease or disorder associated with the target RNA. The unit dose, for example, can be administered by injection (*e.g.*, intravenous or intramuscular), an inhaled  
25 dose, or a topical application. Particularly preferred dosages are less than 2, 1, or 0.1 mg/kg of body weight.

In a preferred embodiment, the unit dose is administered less frequently than once a day, *e.g.*, less than every 2, 4, 8 or 30 days. In another embodiment, the unit dose is not administered with a frequency (*e.g.*, not a regular frequency). For example, the unit dose  
30 may be administered a single time.



In one embodiment, the effective dose is administered with other traditional therapeutic modalities. In one embodiment, the subject has a viral infection and the modality is an antiviral agent other than an iRNA agent, *e.g.*, other than a double-stranded iRNA agent, or sRNA agent,. In another embodiment, the subject has atherosclerosis and the effective dose of an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, is administered in combination with, *e.g.*, after surgical intervention, *e.g.*, angioplasty.

In one embodiment, a subject is administered an initial dose and one or more maintenance doses of an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof). The maintenance dose or doses are generally lower than the initial dose, *e.g.*, one-half less of the initial dose. A maintenance regimen can include treating the subject with a dose or doses ranging from 0.01  $\mu$ g to 1.4 mg/kg of body weight per day, *e.g.*, 10, 1, 0.1, 0.01, 0.001, or 0.00001 mg per kg of bodyweight per day. The maintenance doses are preferably administered no more than once every 5, 10, or 30 days. Further, the treatment regimen may last for a period of time which will vary depending upon the nature of the particular disease, its severity and the overall condition of the patient. In preferred embodiments the dosage may be delivered no more than once per day, *e.g.*, no more than once per 24, 36, 48, or more hours, *e.g.*, no more than once for every 5 or 8 days. Following treatment, the patient can be monitored for changes in his condition and for alleviation of the symptoms of the disease state. The dosage of the compound may either be increased in the event the patient does not respond significantly to current dosage levels, or the dose may be decreased if an alleviation of the symptoms of the disease state is observed, if the disease state has been ablated, or if undesired side-effects are observed.

The effective dose can be administered in a single dose or in two or more doses, as desired or considered appropriate under the specific circumstances. If desired to facilitate repeated or frequent infusions, implantation of a delivery device, *e.g.*, a pump, semi-permanent stent (*e.g.*, intravenous, intraperitoneal, intracisternal or intracapsular), or reservoir may be advisable.

In one embodiment, the iRNA agent pharmaceutical composition includes a plurality of iRNA agent species. In another embodiment, the iRNA agent species has sequences that



are non-overlapping and non-adjacent to another species with respect to a naturally occurring target sequence. In another embodiment, the plurality of iRNA agent species is specific for different naturally occurring target genes. In another embodiment, the iRNA agent is allele specific.

5 In some cases, a patient is treated with a iRNA agent in conjunction with other therapeutic modalities. For example, a patient being treated for a viral disease, *e.g.* an HIV associated disease (*e.g.*, AIDS), may be administered a iRNA agent specific for a target gene essential to the virus in conjunction with a known antiviral agent (*e.g.*, a protease inhibitor or reverse transcriptase inhibitor). In another example, a patient being treated for cancer may be  
10 administered a iRNA agent specific for a target essential for tumor cell proliferation in conjunction with a chemotherapy.

Following successful treatment, it may be desirable to have the patient undergo maintenance therapy to prevent the recurrence of the disease state, wherein the compound of the invention is administered in maintenance doses, ranging from 0.01  $\mu$ g to 100 g per kg of  
15 body weight (see US 6,107,094).

The concentration of the iRNA agent composition is an amount sufficient to be effective in treating or preventing a disorder or to regulate a physiological condition in humans. The concentration or amount of iRNA agent administered will depend on the parameters determined for the agent and the method of administration, *e.g.* nasal, buccal,  
20 pulmonary. For example, nasal formulations tend to require much lower concentrations of some ingredients in order to avoid irritation or burning of the nasal passages. It is sometimes desirable to dilute an oral formulation up to 10-100 times in order to provide a suitable nasal formulation.

Certain factors may influence the dosage required to effectively treat a subject,  
25 including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-  
30 stranded iRNA agent, or sRNA agent, or precursor thereof) can include a single treatment or, preferably, can include a series of treatments. It will also be appreciated that the effective

dosage of a iRNA agent such as a sRNA agent used for treatment may increase or decrease over the course of a particular treatment. Changes in dosage may result and become apparent from the results of diagnostic assays as described herein. For example, the subject can be monitored after administering a iRNA agent composition. Based on information from the  
5 monitoring, an additional amount of the iRNA agent composition can be administered.

Dosing is dependent on severity and responsiveness of the disease condition to be treated, with the course of treatment lasting from several days to several months, or until a cure is effected or a diminution of disease state is achieved. Optimal dosing schedules can be calculated from measurements of drug accumulation in the body of the patient. Persons of  
10 ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates. Optimum dosages may vary depending on the relative potency of individual compounds, and can generally be estimated based on EC50s found to be effective in *in vitro* and *in vivo* animal models. In some embodiments, the animal models include transgenic animals that express a human gene, *e.g.* a gene that produces a target RNA. The transgenic  
15 animal can be deficient for the corresponding endogenous RNA. In another embodiment, the composition for testing includes a iRNA agent that is complementary, at least in an internal region, to a sequence that is conserved between the target RNA in the animal model and the target RNA in a human.

The inventors have discovered that iRNA agents described herein can be administered  
20 to mammals, particularly large mammals such as nonhuman primates or humans in a number of ways.

In one embodiment, the administration of the iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, composition is parenteral, *e.g.* intravenous (*e.g.*, as a bolus or as a diffusible infusion), intradermal, intraperitoneal, intramuscular, intrathecal, intraventricular,  
25 intracranial, subcutaneous, transmucosal, buccal, sublingual, endoscopic, rectal, oral, vaginal, topical, pulmonary, intranasal, urethral or ocular. Administration can be provided by the subject or by another person, *e.g.*, a health care provider. The medication can be provided in measured doses or in a dispenser which delivers a metered dose. Selected modes of delivery are discussed in more detail below.

The invention provides methods, compositions, and kits, for rectal administration or delivery of iRNA agents described herein.

Accordingly, an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes a an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) described herein, *e.g.*, a therapeutically effective amount of a iRNA agent described herein, *e.g.*, a iRNA agent having a double stranded region of less than 40, and preferably less than 30 nucleotides and having one or two 1-3 nucleotide single strand 3' overhangs can be administered rectally, *e.g.*, introduced through the rectum into the lower or upper colon. This approach is particularly useful in the treatment of, inflammatory disorders, disorders characterized by unwanted cell proliferation, *e.g.*, polyps, or colon cancer.

The medication can be delivered to a site in the colon by introducing a dispensing device, *e.g.*, a flexible, camera-guided device similar to that used for inspection of the colon or removal of polyps, which includes means for delivery of the medication.

The rectal administration of the iRNA agent is by means of an enema. The iRNA agent of the enema can be dissolved in a saline or buffered solution. The rectal administration can also by means of a suppository, which can include other ingredients, *e.g.*, an excipient, *e.g.*, cocoa butter or hydropropylmethylcellulose.

Any of the iRNA agents described herein can be administered orally, *e.g.*, in the form of tablets, capsules, gel capsules, lozenges, troches or liquid syrups. Further, the composition can be applied topically to a surface of the oral cavity.

Any of the iRNA agents described herein can be administered buccally. For example, the medication can be sprayed into the buccal cavity or applied directly, *e.g.*, in a liquid, solid, or gel form to a surface in the buccal cavity. This administration is particularly desirable for the treatment of inflammations of the buccal cavity, *e.g.*, the gums or tongue, *e.g.*, in one embodiment, the buccal administration is by spraying into the cavity, *e.g.*, without inhalation, from a dispenser, *e.g.*, a metered dose spray dispenser that dispenses the pharmaceutical composition and a propellant.

Any of the iRNA agents described herein can be administered to ocular tissue. For example, the medications can be applied to the surface of the eye or nearby tissue, *e.g.*, the inside of the eyelid. They can be applied topically, *e.g.*, by spraying, in drops, as an

eyewash, or an ointment. Administration can be provided by the subject or by another person, *e.g.*, a health care provider. The medication can be provided in measured doses or in a dispenser which delivers a metered dose. The medication can also be administered to the interior of the eye, and can be introduced by a needle or other delivery device which can  
5 introduce it to a selected area or structure. Ocular treatment is particularly desirable for treating inflammation of the eye or nearby tissue.

Any of the iRNA agents described herein can be administered directly to the skin. For example, the medication can be applied topically or delivered in a layer of the skin, *e.g.*, by the use of a microneedle or a battery of microneedles which penetrate into the skin, but  
10 preferably not into the underlying muscle tissue. Administration of the iRNA agent composition can be topical. Topical applications can, for example, deliver the composition to the dermis or epidermis of a subject. Topical administration can be in the form of transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids or powders. A composition for topical administration can be formulated as a liposome, micelle,  
15 emulsion, or other lipophilic molecular assembly. The transdermal administration can be applied with at least one penetration enhancer, such as iontophoresis, phonophoresis, and sonophoresis.

Any of the iRNA agents described herein can be administered to the pulmonary system. Pulmonary administration can be achieved by inhalation or by the introduction of a  
20 delivery device into the pulmonary system, *e.g.*, by introducing a delivery device which can dispense the medication. A preferred method of pulmonary delivery is by inhalation. The medication can be provided in a dispenser which delivers the medication, *e.g.*, wet or dry, in a form sufficiently small such that it can be inhaled. The device can deliver a metered dose of medication. The subject, or another person, can administer the medication.

25 Pulmonary delivery is effective not only for disorders which directly affect pulmonary tissue, but also for disorders which affect other tissue.

iRNA agents can be formulated as a liquid or nonliquid, *e.g.*, a powder, crystal, or aerosol for pulmonary delivery.

Any of the iRNA agents described herein can be administered nasally. Nasal  
30 administration can be achieved by introduction of a delivery device into the nose, *e.g.*, by introducing a delivery device which can dispense the medication. Methods of nasal delivery

include spray, aerosol, liquid, *e.g.*, by drops, or by topical administration to a surface of the nasal cavity. The medication can be provided in a dispenser with delivery of the medication, *e.g.*, wet or dry, in a form sufficiently small such that it can be inhaled. The device can deliver a metered dose of medication. The subject, or another person, can administer the  
5 medication.

Nasal delivery is effective not only for disorders which directly affect nasal tissue, but also for disorders which affect other tissue

iRNA agents can be formulated as a liquid or nonliquid, *e.g.*, a powder, crystal, or for nasal delivery.

10 An iRNA agent can be packaged in a viral natural capsid or in a chemically or enzymatically produced artificial capsid or structure derived therefrom.

The dosage of a pharmaceutical composition including a iRNA agent can be administered in order to alleviate the symptoms of a disease state, *e.g.*, cancer or a cardiovascular disease. A subject can be treated with the pharmaceutical composition by any  
15 of the methods mentioned above.

Gene expression in a subject can be modulated by administering a pharmaceutical composition including an iRNA agent.

A subject can be treated by administering a defined amount of an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent  
20 which can be processed into a sRNA agent) composition that is in a powdered form, *e.g.*, a collection of microparticles, such as crystalline particles. The composition can include a plurality of iRNA agents, *e.g.*, specific for one or more different endogenous target RNAs. The method can include other features described herein.

A subject can be treated by administering a defined amount of an iRNA agent  
25 composition that is prepared by a method that includes spray-drying, *i.e.* atomizing a liquid solution, emulsion, or suspension, immediately exposing the droplets to a drying gas, and collecting the resulting porous powder particles. The composition can include a plurality of iRNA agents, *e.g.*, specific for one or more different endogenous target RNAs. The method can include other features described herein.

30 The iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA



which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof), can be provided in a powdered, crystallized or other finely divided form, with or without a carrier, *e.g.*, a micro- or nano-particle suitable for inhalation or other pulmonary delivery. This can include providing an aerosol preparation, *e.g.*, an aerosolized spray-dried composition. The aerosol composition can be provided in and/or dispensed by a metered dose delivery device.

The subject can be treated for a condition treatable by inhalation, *e.g.*, by aerosolizing a spray-dried iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) composition and inhaling the aerosolized composition. The iRNA agent can be an sRNA. The composition can include a plurality of iRNA agents, *e.g.*, specific for one or more different endogenous target RNAs. The method can include other features described herein.

A subject can be treated by, for example, administering a composition including an effective/defined amount of an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof), wherein the composition is prepared by a method that includes spray-drying, lyophilization, vacuum drying, evaporation, fluid bed drying, or a combination of these techniques

In another aspect, the invention features a method that includes: evaluating a parameter related to the abundance of a transcript in a cell of a subject; comparing the evaluated parameter to a reference value; and if the evaluated parameter has a preselected relationship to the reference value (*e.g.*, it is greater), administering a iRNA agent (or a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes a iRNA agent or precursor thereof) to the subject. In one embodiment, the iRNA agent includes a sequence that is complementary to the evaluated transcript. For example, the parameter can be a direct measure of transcript levels, a measure of a protein level, a disease or disorder symptom or characterization (*e.g.*, rate of cell proliferation and/or tumor mass, viral load,)

In another aspect, the invention features a method that includes: administering a first amount of a composition that comprises an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) to a subject, wherein the iRNA agent includes a strand substantially complementary to a target nucleic acid; evaluating an activity associated with a protein encoded by the target nucleic acid; wherein the evaluation is used to determine if a second amount should be administered. In a preferred embodiment the method includes administering a second amount of the composition, wherein the timing of administration or dosage of the second amount is a function of the evaluating. The method can include other features described herein.

In another aspect, the invention features a method of administering a source of a double-stranded iRNA agent (ds iRNA agent) to a subject. The method includes administering or implanting a source of a ds iRNA agent, *e.g.*, a sRNA agent, that (a) includes a double-stranded region that is 19-25 nucleotides long, preferably 21-23 nucleotides, (b) is complementary to a target RNA (*e.g.*, an endogenous RNA or a pathogen RNA), and, optionally, (c) includes at least one 3' overhang 1-5 nt long. In one embodiment, the source releases ds iRNA agent over time, *e.g.* the source is a controlled or a slow release source, *e.g.*, a microparticle that gradually releases the ds iRNA agent. In another embodiment, the source is a pump, *e.g.*, a pump that includes a sensor or a pump that can release one or more unit doses.

In one aspect, the invention features a pharmaceutical composition that includes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) including a nucleotide sequence complementary to a target RNA, *e.g.*, substantially and/or exactly complementary. The target RNA can be a transcript of an endogenous human gene. In one embodiment, the iRNA agent (a) is 19-25 nucleotides long, preferably 21-23 nucleotides, (b) is complementary to an endogenous target RNA, and, optionally, (c) includes at least one 3' overhang 1-5 nt long. In one embodiment, the pharmaceutical composition can be an emulsion, microemulsion, cream, jelly, or liposome.

In one example the pharmaceutical composition includes an iRNA agent mixed with a topical delivery agent. The topical delivery agent can be a plurality of microscopic vesicles. The microscopic vesicles can be liposomes. In a preferred embodiment the liposomes are cationic liposomes.

5 In another aspect, the pharmaceutical composition includes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) admixed with a topical penetration enhancer. In one embodiment, the topical penetration enhancer is a fatty acid.  
10 The fatty acid can be arachidonic acid, oleic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a C<sub>1-10</sub> alkyl ester, monoglyceride, diglyceride or pharmaceutically acceptable salt thereof.

15 In another embodiment, the topical penetration enhancer is a bile salt. The bile salt can be cholic acid, dehydrocholic acid, deoxycholic acid, glucolic acid, glycholic acid, glycodeoxycholic acid, taurocholic acid, taurodeoxycholic acid, chenodeoxycholic acid, ursodeoxycholic acid, sodium tauro-24,25-dihydro-fusidate, sodium glycodihydrofusidate, polyoxyethylene-9-lauryl ether or a pharmaceutically acceptable salt thereof.

20 In another embodiment, the penetration enhancer is a chelating agent. The chelating agent can be EDTA, citric acid, a salicylate, a N-acyl derivative of collagen, laureth-9, an N-amino acyl derivative of a beta-diketone or a mixture thereof.

In another embodiment, the penetration enhancer is a surfactant, *e.g.*, an ionic or nonionic surfactant. The surfactant can be sodium lauryl sulfate, polyoxyethylene-9-lauryl  
25 ether, polyoxyethylene-20-cetyl ether, a perfluorchemical emulsion or mixture thereof.

In another embodiment, the penetration enhancer can be selected from a group consisting of unsaturated cyclic ureas, 1-alkyl-alkones, 1-alkenylazacyclo-alkanones, steroidal anti-inflammatory agents and mixtures thereof. In yet another embodiment the penetration enhancer can be a glycol, a pyrrol, an azone, or a terpenes.

30 In one aspect, the invention features a pharmaceutical composition including an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a

larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) in a form suitable for oral delivery. In one embodiment, oral delivery can be used to deliver an iRNA agent composition to a cell or a region of the gastro-intestinal tract, *e.g.*, small intestine, colon (*e.g.*, to treat a colon cancer), and so forth. The oral delivery form can be tablets, capsules or gel capsules. In one embodiment, the iRNA agent of the pharmaceutical composition modulates expression of a cellular adhesion protein, modulates a rate of cellular proliferation, or has biological activity against eukaryotic pathogens or retroviruses. In another embodiment, the pharmaceutical composition includes an enteric material that substantially prevents dissolution of the tablets, capsules or gel capsules in a mammalian stomach. In a preferred embodiment the enteric material is a coating. The coating can be acetate phthalate, propylene glycol, sorbitan monoleate, cellulose acetate trimellitate, hydroxy propyl methylcellulose phthalate or cellulose acetate phthalate.

In another embodiment, the oral dosage form of the pharmaceutical composition includes a penetration enhancer. The penetration enhancer can be a bile salt or a fatty acid. The bile salt can be ursodeoxycholic acid, chenodeoxycholic acid, and salts thereof. The fatty acid can be capric acid, lauric acid, and salts thereof.

In another embodiment, the oral dosage form of the pharmaceutical composition includes an excipient. In one example the excipient is polyethyleneglycol. In another example the excipient is precirol.

In another embodiment, the oral dosage form of the pharmaceutical composition includes a plasticizer. The plasticizer can be diethyl phthalate, triacetin dibutyl sebacate, dibutyl phthalate or triethyl citrate.

In one aspect, the invention features a pharmaceutical composition including an iRNA agent and a delivery vehicle. In one embodiment, the iRNA agent is (a) is 19-25 nucleotides long, preferably 21-23 nucleotides, (b) is complementary to an endogenous target RNA, and, optionally, (c) includes at least one 3' overhang 1-5 nucleotides long.

In one embodiment, the delivery vehicle can deliver an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) to a cell by a topical route of



administration. The delivery vehicle can be microscopic vesicles. In one example the microscopic vesicles are liposomes. In a preferred embodiment the liposomes are cationic liposomes. In another example the microscopic vesicles are micelles. In one aspect, the invention features a pharmaceutical composition including an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) in an injectable dosage form. In one embodiment, the injectable dosage form of the pharmaceutical composition includes sterile aqueous solutions or dispersions and sterile powders. In a preferred embodiment the sterile solution can include a diluent such as water; saline solution; fixed oils, polyethylene glycols, glycerin, or propylene glycol.

In one aspect, the invention features a pharmaceutical composition including an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) in oral dosage form. In one embodiment, the oral dosage form is selected from the group consisting of tablets, capsules and gel capsules. In another embodiment, the pharmaceutical composition includes an enteric material that substantially prevents dissolution of the tablets, capsules or gel capsules in a mammalian stomach. In a preferred embodiment the enteric material is a coating. The coating can be acetate phthalate, propylene glycol, sorbitan monoleate, cellulose acetate trimellitate, hydroxy propyl methyl cellulose phthalate or cellulose acetate phthalate. In one embodiment, the oral dosage form of the pharmaceutical composition includes a penetration enhancer, *e.g.*, a penetration enhancer described herein.

In another embodiment, the oral dosage form of the pharmaceutical composition includes an excipient. In one example the excipient is polyethyleneglycol. In another example the excipient is precirol.

In another embodiment, the oral dosage form of the pharmaceutical composition includes a plasticizer. The plasticizer can be diethyl phthalate, triacetin dibutyl sebacate, dibutyl phthalate or triethyl citrate.

In one aspect, the invention features a pharmaceutical composition including an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a



larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) in a rectal dosage form. In one embodiment, the rectal dosage form is an enema. In another embodiment, the rectal dosage form is a suppository.

5 In one aspect, the invention features a pharmaceutical composition including an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) in a vaginal dosage form. In one embodiment, the vaginal dosage form is a suppository. In  
10 another embodiment, the vaginal dosage form is a foam, cream, or gel.

In one aspect, the invention features a pharmaceutical composition including an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) in a  
15 pulmonary or nasal dosage form. In one embodiment, the iRNA agent is incorporated into a particle, *e.g.*, a macroparticle, *e.g.*, a microsphere. The particle can be produced by spray drying, lyophilization, evaporation, fluid bed drying, vacuum drying, or a combination thereof. The microsphere can be formulated as a suspension, a powder, or an implantable solid.

20 In one aspect, the invention features a spray-dried iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof) composition suitable for inhalation by a subject, including: (a) a therapeutically effective amount of a iRNA agent  
25 suitable for treating a condition in the subject by inhalation; (b) a pharmaceutically acceptable excipient selected from the group consisting of carbohydrates and amino acids; and (c) optionally, a dispersibility-enhancing amount of a physiologically-acceptable, water-soluble polypeptide.

In one embodiment, the excipient is a carbohydrate. The carbohydrate can be  
30 selected from the group consisting of monosaccharides, disaccharides, trisaccharides, and polysaccharides. In a preferred embodiment the carbohydrate is a monosaccharide selected

from the group consisting of dextrose, galactose, mannitol, D-mannose, sorbitol, and sorbose. In another preferred embodiment the carbohydrate is a disaccharide selected from the group consisting of lactose, maltose, sucrose, and trehalose.

In another embodiment, the excipient is an amino acid. In one embodiment, the amino acid is a hydrophobic amino acid. In a preferred embodiment the hydrophobic amino acid is selected from the group consisting of alanine, isoleucine, leucine, methionine, phenylalanine, proline, tryptophan, and valine. In yet another embodiment the amino acid is a polar amino acid. In a preferred embodiment the amino acid is selected from the group consisting of arginine, histidine, lysine, cysteine, glycine, glutamine, serine, threonine, tyrosine, aspartic acid and glutamic acid.

In one embodiment, the dispersibility-enhancing polypeptide is selected from the group consisting of human serum albumin,  $\alpha$ -lactalbumin, trypsinogen, and polyalanine.

In one embodiment, the spray-dried iRNA agent composition includes particles having a mass median diameter (MMD) of less than 10 microns. In another embodiment, the spray-dried iRNA agent composition includes particles having a mass median diameter of less than 5 microns. In yet another embodiment the spray-dried iRNA agent composition includes particles having a mass median aerodynamic diameter (MMAD) of less than 5 microns.

In certain other aspects, the invention provides kits that include a suitable container containing a pharmaceutical formulation of an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof). In certain embodiments the individual components of the pharmaceutical formulation may be provided in one container.

Alternatively, it may be desirable to provide the components of the pharmaceutical formulation separately in two or more containers, *e.g.*, one container for an iRNA agent preparation, and at least another for a carrier compound. The kit may be packaged in a number of different configurations such as one or more containers in a single box. The different components can be combined, *e.g.*, according to instructions provided with the kit. The components can be combined according to a method described herein, *e.g.*, to prepare and administer a pharmaceutical composition. The kit can also include a delivery device.

In another aspect, the invention features a device, *e.g.*, an implantable device, wherein the device can dispense or administer a composition that includes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, (*e.g.*, a precursor, *e.g.*, a larger iRNA agent which can be processed into a sRNA agent, or a DNA which encodes an iRNA agent, *e.g.*, a double-stranded iRNA agent, or sRNA agent, or precursor thereof), *e.g.*, a iRNA agent that silences an endogenous transcript. In one embodiment, the device is coated with the composition. In another embodiment the iRNA agent is disposed within the device. In another embodiment, the device includes a mechanism to dispense a unit dose of the composition. In other embodiments the device releases the composition continuously, *e.g.*, by diffusion. Exemplary devices include stents, catheters, pumps, artificial organs or organ components (*e.g.*, artificial heart, a heart valve, etc.), and sutures.

As used herein, the term “crystalline” describes a solid having the structure or characteristics of a crystal, *i.e.*, particles of three-dimensional structure in which the plane faces intersect at definite angles and in which there is a regular internal structure. The compositions of the invention may have different crystalline forms. Crystalline forms can be prepared by a variety of methods, including, for example, spray drying.

The invention is further illustrated by the following examples, which should not be construed as further limiting.

20

## EXAMPLES

### **Example 1: Inhibition of endogenous ApoM gene expression in mice**

Apolipoprotein M (ApoM) is a human apolipoprotein predominantly present in high-density lipoprotein (HDL) in plasma. ApoM is reported to be expressed exclusively in liver and in kidney (Xu N *et al.*, Biochem J Biol Chem 1999 Oct 29;274(44):31286-90). Mouse ApoM is a 21kD membrane associated protein, and, in serum, the protein is associated with HDL particles. ApoM gene expression is regulated by the transcription factor hepatocyte nuclear factor 1 alpha (Hnf-1 $\alpha$ ), as Hnf-1 $\alpha$ <sup>-/-</sup> mice are ApoM deficient. In humans, mutations in the HNF-1 alpha gene represent a common cause of maturity-onset diabetes of the young (MODY).

A variety of test iRNAs were synthesized to target the mouse ApoM gene. This gene was chosen in part because of its high expression levels and exclusive activity in the liver and kidney.

Three different classes of dsRNA agents were synthesized, each class having different  
5 modifications and features at the 5' and 3' ends, see Table 4.

**Table 4**

**Targeted ORF's**

5	5	The23mer: AAGTTTGGGCAGCTCTGCTCT	(SEQ ID NO:6708)
	19	The23mer: AAGTGGACATACCGATTGACT	(SEQ ID NO:6709)
	25	The23mer: AACTCAGAACTGAAGGGCGCC	(SEQ ID NO:6710)
10	27	The23mer: AAGGGCGCCCAGACATGAAAA	(SEQ ID NO:6711)
		3'-UTR (beginning at 645)	
	42:	AAGATAGGAGCCCAGCTTCGA	(SEQ ID NO:6712)

15

**Class I**

21-nt iRNAs, t, deoxythymidine; p, phosphate

	pGUUUGGGCAGCUCUGCUCUtt	(SEQ ID NO:6712) #1
20	pAGAGCAGAGCUGCCCAAActt	(SEQ ID NO:6713)
	pGUGGACAUACCGAUUGACUtt	(SEQ ID NO:6714) #2
	pAGUCAAUUCGGUAUGUCCActt	(SEQ ID NO:6715)
25	pCUCAGAACUGAAGGGCGCctt	(SEQ ID NO:6716) #3
	pGGCGCCCUUCAGUUCUGAGtt	(SEQ ID NO:6717)
	pGAUAGGAGCCCAGCUUCGAtt	(SEQ ID NO:6718) #4
	pUCGAAGCUGGGCUCCUAUCtt	(SEQ ID NO:6719)

30



Class II

21-nt iRNAs, t, deoxythymidine; p, phosphate; ps, thiophosphate

- 5 pGUUUGGGCAGCUCUGCUCpsUpstpst (SEQ ID NO:6720) #11  
 pAGAGCAGAGCUGCCCAApsCpstpst (SEQ ID NO:6721)
- pGUGGACAUACCGAUUGACpsUpstpst (SEQ ID NO:6722) #13  
 pAGUCAAUUCGGUAUGUCCApCpstpst (SEQ ID NO:6723)
- 10 pCUCAGAACUGAAGGGCGCpsCpstpst (SEQ ID NO:6724) #15  
 pGGCGCCCUUCAGUUCUGApGpstpst (SEQ ID NO:6725)
- pGAUAGGAGCCCAGCUUCGpsApstpst (SEQ ID NO:6726) #17  
 15 pUCGAAGCUGGGCUCCUAUpsCpstpst (SEQ ID NO:6727)

Class III

23-nt antisense, 21-nt sense, blunt-ended 5'-as

- 20 GUUUGGGCAGCUCUGCUCUCU (SEQ ID NO:6728) #19  
 AGAGAGCAGAGCUGCCCAAACUU (SEQ ID NO:6729)
- GUGGACAUACCGAUUGACUGA (SEQ ID NO:6730) #21  
 UCAGUCAAUUCGGUAUGUCCACUU (SEQ ID NO:6731)
- 25 CUCAGAACUGAAGGGCGCCCA (SEQ ID NO:6732) #23  
 PUGGGCGCCCUUCAGUUCUGAGUU (SEQ ID NO:6733)
- GAUAGGAGCCCAGCUUCGAGU (SEQ ID NO:6734) #25  
 30 ACUCGAAGCUGGGCUCCUAUCUU (SEQ ID NO:6735)

Class I dsRNAs consisted of 21 nucleotide paired sense and antisense strands. The sense and antisense strands were each phosphorylated at their 5' ends. The double stranded

235

region was 19 nucleotides long and consisted of ribonucleotides. The 3' end of each strand created a two nucleotide overhang consisting of two deoxyribonucleotide thymidines. See constructs #1-4 in Table 4.

Class II dsRNAs were also 21 nucleotides long, with a 19 nucleotide double strand region. The sense and antisense strands were each phosphorylated at their 5' ends. The three 3' terminal nucleotides of the sense and antisense strands were phosphorothioate deoxyribonucleotides, and the two terminal phosphorothioate thymidines were unpaired, creating a 3' overhang region at each end of the iRNA molecule. See constructs 11, 13, 15, and 17 in Table 4.

Class III dsRNAs included a 23 ribonucleotide antisense strand and a 21 ribonucleotide sense strand, to form a construct having a blunt 5' and a 3' overhang region. See constructs 19, 21, 23, and 25 in Table 4.

Within each of the three classes of iRNAs, the four dsRNA molecules were designed to target four different regions of the ApoM transcript. dsRNAs 1, 11, and 19 targeted the 5' end of the open reading frame (ORF). dsRNAs 2, 13, and 21, and 3, 15, and 23, targeted two internal regions (one 5' proximal and one 3' proximal) of the ORF, and the 4, 17, and 25 iRNA constructs targeted to a region of the 3' untranslated sequence (3' UTS) of the ApoM mRNA. This is summarized in Table 5.

**Table 5. iRNA molecules targeted to mouse ApoM**

	iRNA targeted to 5' end of ORF	iRNA targeted to middle ORF (5' proximal)	iRNA targeted to middle ORF (3' proximal)	iRNA targeted to 3'UTS
Class I	1	2	3	4
Class II	11	13	15	17
Class III	19	21	23	25

CD1 mice (6-8 weeks old, ~35g) were administered one of the test iRNAs in PBS solution. Two hundred micrograms of iRNA in a volume of solution equal to 10% body weight (~5.7mg iRNA/kg mouse) was administered by the method of high pressure tail vein injection, over a 10-20 sec. time interval. After a 24h recovery period, a second injection was performed using the same dose and mode of administration as the first injection, and

following another 24h, a third and final injection was administered, also using the same dose and mode of administration. After a final 24h recovery, the mouse was sacrificed, serum was collected and the liver and kidney harvested to assay for an effect on ApoM gene expression. Expression was monitored by quantitative RT-PCR and Western blot analyses. This  
5 experiment was repeated for each of the iRNAs listed in table 4.

Class I iRNAs did not alter ApoM RNA levels in mice, as indicated by quantitative RT-PCR. This is in contrast to the effect of these iRNAs in cultured HepG2 cells. Cells cotransfected with a plasmid expressing exogenous ApoM RNA under a CMV promoter and a class I iRNA demonstrated a 25% or greater reduction in ApoM RNA concentrations as  
10 compared to control transfections. The iRNA molecules 1, 2 and 3 each caused a 75% decrease in exogenous ApoM mRNA levels.

Class II iRNAs reduced liver and kidney ApoM mRNA levels by ~30-85%. The iRNA molecule "13" elicited the most dramatic reduction in mRNA levels; quantitative RT-PCR indicated a decrease of about 85% in liver tissue. Serum ApoM protein levels were also  
15 reduced as was evidenced by Western blot analysis. The iRNAs 11, 13 and 15, reduced protein levels by about 50%, while iRNA 17 had the mildest effect, reducing levels only by ~15-20%.

Class III iRNAs (constructs 19, 21, and 23) reduced serum Apo levels by ~40-50%.

To determine the effect of dosage on iRNA mediated ApoM inhibition, the  
20 experiment described above was repeated with three injections of 50µg iRNA "11" (~1.4mg iRNA/kg mouse). This lower dosage of iRNA resulted in a reduction of serum ApoM levels of about 50%. This is compared with the reduction seen with the 200µg injections, which reduced serum levels by 25-45%. These results indicated the lower dosage amounts of iRNAs were effective.

25 In an effort to increase iRNA uptake by cells, iRNAs were precomplexed with lipofectamine prior to tail vein injections. ApoM protein levels were about 50% of wildtype levels in mice injected with iRNA "11" when the molecules were preincubated with lipofectamine; ApoM levels were also about 50% of wildtype when mice were injected with iRNA "11" that was not precomplexed with lipofectamine.

These experiments revealed that modified iRNAs can greatly influence RNAi-mediated gene silencing. As demonstrated herein, modifications including phosphorothioate nucleotides are particularly effective at decreasing target protein levels.

5

**Example 2: apoB protein as a therapeutic target for lipid-based diseases**

Apolipoprotein B (apoB) is a candidate target gene for the development of novel therapies for lipid-based diseases.

Methods described herein can be used to evaluate the efficacy of a particular siRNA as a therapeutic tool for treating lipid metabolism disorders resulting elevated apoB levels. Use of siRNA duplexes to selectively bind and inactivate the target apoB mRNA is an approach to treat these disorders.

Two approaches:

i) Inhibition of apoB in *ex-vivo* models by transfecting siRNA duplexes homologous to human apoB mRNA in a human hepatoma cell line (Hep G2) and monitor the level of the protein and the RNA using the Western blotting and RT-PCR methods, respectively. siRNA molecules that efficiently inhibit apoB expression will be tested for similar effects *in vivo*.

ii) *In vivo* trials using an apoB transgenic mouse model (apoB100 Transgenic Mice, C57BL/6NTac-TgN (APOB100), Order Model #'s:1004-T (hemizygotes), B6 (control)). siRNA duplexes are designed to target apoB-100 or CETP/apoB double transgenic mice which express both cholesteryl ester transfer protein (CETP) and apoB. The effect of the siRNA on gene expression *in vivo* can be measured by monitoring the HDL/LDL cholesterol level in serum. The results of these experiments would indicate the therapeutic potential of siRNAs to treat lipid-based diseases, including hypercholesterolemia, HDL/LDL cholesterol imbalance, familial combined hyperlipidemia, and acquired hyperlipidemia.

*Background* Fats, in the form of triglycerides, are ideal for energy storage because they are highly reduced and anhydrous. An adipocyte (or fat cell) consists of a nucleus, a cell membrane, and triglycerides, and its function is to store triglycerides.

The lipid portion of the human diet consists largely of triglycerides and cholesterol (and its esters). These must be emulsified and digested to be absorbed. Specifically, fats

(triacylglycerols) are ingested. Bile (bile acids, salts, and cholesterol), which is made in the liver, is secreted by the gall bladder. Pancreatic lipase digests the triglycerides to fatty acids, and also digests di-, and mono-acylglycerols, which are absorbed by intestinal epithelial cells and then are resynthesized into triacylglycerols once inside the cells. These triglycerides and  
5 some cholesterol are combined with apolipoproteins to produce chylomicrons. Chylomicrons consist of approximately 95% triglycerides. The chylomicrons transport fatty acids to peripheral tissues. Any excess fat is stored in adipose tissue.

Lipid transport and clearance from the blood into cells, and from the cells into the blood and the liver, is mediated by the lipoprotein transport proteins. This class of  
10 approximately 17 proteins can be divided into three groups: Apolipoproteins, lipoprotein processing proteins, and lipoprotein receptors.

Apolipoproteins coat lipoprotein particles, and include the A-I, A-II, A-IV, B, CI, CII, CIII, D, E, Apo(a) proteins. Lipoprotein processing proteins include lipoprotein lipase, hepatic lipase, lecithin cholesterol acyltransferase and cholesterol ester transfer protein.  
15 Lipoprotein receptors include the low density lipoprotein (LDL) receptor, chylomicron-remnant receptor (the LDL receptor like protein or LDL receptor related protein - LRP) and the scavenger receptor.

*Lipoprotein Metabolism* Since the triglycerides, cholesterol esters, and cholesterol absorbed  
20 into the small intestine are not soluble in aqueous medium, they must be combined with suitable proteins (apolipoproteins) in order to prevent them from forming large oil droplets. The resulting lipoproteins undergo a type of metabolism as they pass through the bloodstream and certain organs (notably the liver).

Also synthesized in the liver is high density lipoprotein (HDL), which contains the  
25 apoproteins A-1, A-2, C-1, and D; HDL collects cholesterol from peripheral tissues and blood vessels and returns it to the liver. LDL is taken up by specific cell surface receptors into an endosome, which fuses with a lysosome where cholesterol ester is converted to free cholesterol. The apoproteins (including apo B-100) are digested to amino acids. The receptor protein is recycled to the cell membrane.

30 The free cholesterol formed by this process has two fates. First, it can move to the endoplasmic reticulum (ER), where it can inhibit HMG-CoA reductase, the synthesis of



HMG-CoA reductase, and the synthesis of cell surface receptors for LDL. Also in the ER, cholesterol can speed up the degradation of HMG-CoA reductase. The free cholesterol can also be converted by acyl-CoA and acyl transferase (ACAT) to cholesterol esters, which form oil droplets.

5           ApoB is the major apolipoprotein of chylomicrons of very low density lipoproteins (VLDL, which carry most of the plasma triglyceride) and low density lipoprotein (LDL, which carry most of the plasma cholesterol). ApoB exists in human plasma in two isoforms, apoB-48 and apoB-100.

          ApoB-100 is the major physiological ligand for the LDL receptor. The ApoB  
10 precursor has 4563 amino acids, and the mature apoB-100 has 4536 amino acid residues. The LDL-binding domain of ApoB-100 is proposed to be located between residues 3129 and 3532. ApoB-100 is synthesized in the liver and is required for the assembly of very low density lipoproteins VLDL and for the preparation of apoB-100 to transport triglycerides (TG) and cholesterol from the liver to other tissues. ApoB-100 does not interchange between  
15 lipoprotein particles, as do the other lipoproteins, and it is found in IDL and LDL particles. After the removal of apolipoproteins A, E and C, apoB is incorporation into VLDL by hepatocytes. ApoB-48 is present in chylomicrons and plays an essential role in the intestinal absorption of dietary fats. ApoB-48 is synthesized in the small intestine. It comprises the N-terminal 48% of apoB-100 and is produced by a posttranscriptional apoB-100 mRNA editing  
20 event at codon 2153 (C to U). This editing event is a product of the apoBEC-1b enzyme, which is expressed in the intestine. This editing event creates a stop codon instead of a glutamine codon, and therefore apoB-48, instead of apoB-100 is expressed in the intestine (apoB-100 is expressed in the liver).

          There is also strong evidence that plasma apoB levels may be a better index of the  
25 risk of coronary artery disease (CAD) than total or LDL cholesterol levels. Clinical studies have demonstrated the value of measuring apoB in hypertriglyceridemic, hypercholesterolemic and normalipidemic subjects.

**Table 6. Reference Range Lipid level in the Blood**

<b>Lipid</b>	<b>Range (mmols/ L)</b>
Plasma Cholesterol	3.5-6.5
Low density lipoprotein	1.55-4.4
Very low density lipoprotein	0.128-0.645
High density lipoprotein/ triglycerides	0.5-2.1
<b>Total lipid</b>	<b>4.0-10g / L</b>

*Molecular genetics of lipid metabolism in both humans and induced mutant mouse models*

5 Elevated plasma levels of LDL and apoB are associated with a higher risk for atherosclerosis and coronary heart disease, a leading cause of mortality. ApoB is the mandatory constituent of LDL particles. In addition to its role in lipoprotein metabolism, apoB has also been implicated as a factor in male infertility and fetal development. Furthermore, two quantitative trait loci regulating plasma apoB levels have been discovered, through the use of  
10 transgenic mouse models. Future experiments will facilitate the identification of human orthologous genes encoding regulators of plasma apoB levels. These loci are candidate therapeutic targets for human disorders characterized by altered plasma apoB levels. Such disorders include non-apoB linked hypobetalipoproteinemia and familial combined hyperlipidemia. The identification of these genetic loci would also reveal possible new  
15 pathways involved in the regulation of apoB secretion, potentially providing novel sites for pharmacological therapy.

*Diseases and Clinical Pharmacology* Familial combined hyperlipemia (FCHL) affects an estimated one in 10 Americans. FCHL can cause premature heart disease.

20 *Familial Hypercholesterolemia (high level of apo B)* A common genetic disorder of lipid metabolism. Familial hypercholesterolemia is characterized by elevated serum TC in association with xanthelasma, tendon and tuberous xanthomas, accelerated atherosclerosis, and early death from myocardial infarction (MI). It is caused by absent or defective LDL cell receptors, resulting in delayed LDL clearance, an increase in plasma LDL levels, and an  
25 accumulation of LDL cholesterol in macrophages over joints and pressure points, and in blood vessels.

*Atherosclerosis (high level of apo B)* Atherosclerosis develops as a deposition of cholesterol and fat in the arterial wall due to disturbances in lipid transport and clearance from the blood into cells and from the cells to blood and the liver.

5           Clinical studies have demonstrated that elevation of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and apoB-100 promote human atherosclerosis. Similarly, decreased levels of high – density lipoprotein cholesterol (HDL-C) are associated with the development of atherosclerosis.

ApoB may be factor in the genetic cause of high cholesterol.

10   *The risk of coronary artery disease (CAD) (high level of apo B)* Cardiovascular disease, including coronary heart disease and stroke, is a leading cause of death and disability. The major risk factors include age, gender, elevated low-density lipoprotein cholesterol blood levels, decreased high-density lipoprotein cholesterol levels, cigarette smoking, hypertension, and diabetes. Emerging risk factors include elevated lipoprotein (a), remnant lipoproteins,  
15   and C reactive protein. Dietary intake, physical activity and genetics also impact cardiovascular risk. Hypertension and age are the major risk factors for stroke.

Abetalipoproteinemia, an inherited human disease characterized by a near-complete absence of apoB-containing lipoproteins in the plasma, is caused by mutations in the gene for microsomal triglyceride transfer protein (MTP).

20

*Model for human atherosclerosis (Lipoprotein A transgenic mouse)* Numerous studies have demonstrated that an elevated plasma level of lipoprotein(a) (Lp(a)) is a major independent risk factor for coronary heart disease (CHD). Current therapies, however, have little or no effect on apo(a) levels and the homology between apo(a) and plasminogen presents barriers  
25   to drug development. Lp(a) particles consist of apo(a) and apoB-100 proteins, and they are found only in primates and the hedgehog. The development of LPA transgenic mouse requires the creation of animals that express both human apoB and apo(a) transgenes to achieve assembly of LP(a). An atherosclerosis mouse model would facilitate the study of the disease process and factors influencing it, and further would facilitate the development of  
30   therapeutic or preventive agents. There are several strategies for gene-oriented therapy. For

example, the missing or non-functional gene can be replaced, or unwanted gene activity can be inhibited.

*Model for lipid Metabolism and Atherosclerosis* DNX Transgenic Sciences has demonstrated that both CETP/ApoB and ApoB transgenic mice develop atherosclerotic plaques.

*Model for apoB-100 overexpression* The apoB-100 transgenic mice express high levels of human apoB-100. They consequently demonstrate elevated serum levels of LDL cholesterol. After 6 months on a high-fat diet, the mice develop significant foam cell accumulation under the endothelium and within the media, as well as cholesterol crystals and fibrotic lesions.

*Model for Cholesteryl ester transfer protein over expression* The apoB-100 transgenic mice express the human enzyme, CETP, and consequently demonstrate a dramatically reduced level of serum HDL cholesterol.

*Model for apoB-100 and CETP overexpression* The apoB-100 transgenic mice express both CETP and apoB-100, resulting in mice with a human like serum HDL/LDL distribution. Following 6 months on a high-fat diet these mice develop significant foam cell accumulation underlying the endothelium and within the media, as well as cholesterol crystals and fibrotic lesions.

*ApoB100 Transgenic Mice (Order Model #'s: 1004-T (hemizygotes), B6 (control))*  
These mice express high levels of human apoB-100, resulting in mice with elevated serum levels of LDL cholesterol. These mice are useful in identifying and evaluating compounds to reduce elevated levels of LDL cholesterol and the risk of atherosclerosis. When fed a high fat cholesterol diet, these mice develop significant foam cell accumulation under the endothelium and within the media, and have significantly more complex atherosclerotic lesions than control animals.

30

*Double Transgenic Mice, CETP/ApoB100 (Order Model #: 1007-TT)* These mice express both CETP and apoB-100, resulting in a human-like serum HDL/LDL distribution. These mice are useful for evaluating compounds to treat hypercholesterolemia or HDL/LDL cholesterol imbalance to reduce the risk of developing atherosclerosis. When fed a high fat high cholesterol diet, these mice develop significant foam cell accumulation underlying the endothelium and within the media, and have significantly more complex atherosclerotic lesions than control animals.

*ApoE gene knockout mouse* Homozygous apoE knockout mice exhibit strong hypercholesterolemia, primarily due to elevated levels of VLDL and IDL caused by a defect in lipoprotein clearance from plasma. These mice develop atherosclerotic lesions which progress with age and resemble human lesions (Zhang *et al.*, *Science* 258:46-71, 1992; Plump *et al.*, *Cell* 71:343-353, 1992; Nakashima *et al.*, *Arterioscler Thromp.* 14:133-140, 1994; Reddick *et al.*, *Arterioscler Tromb.* 14:141-147, 1994). These mice are a promising model for studying the effect of diet and drugs on atherosclerosis.

Low density lipoprotein receptor (LDLR) mediates lipoprotein clearance from plasma through the recognition of apoB and apoE on the surface of lipoprotein particles. Humans, who lack or have a decreased number of the LDL receptors, have familial hypercholesterolemia and develop CHD at an early age.

20

*ApoE Knockout Mice (Order Model #: APOE-M)* The apoE knockout mouse was created by gene targeting in embryonic stem cells to disrupt the apoE gene. ApoE, a glycoprotein, is a structural component of very low density lipoprotein (VLDL) synthesized by the liver and intestinally synthesized chylomicrons. It is also a constituent of a subclass of high density lipoproteins (HDLs) involved in cholesterol transport activity among cells. One of the most important roles of apoE is to mediate high affinity binding of chylomicrons and VLDL particles that contain apoE to the low density lipoprotein (LDL) receptor. This allows for the specific uptake of these particles by the liver which is necessary for transport preventing the accumulation in plasma of cholesterol-rich remnants. The homozygous inactivation of the apoE gene results in animals that are devoid of apoE in their sera. The mice appear to develop normally, but they exhibit five times the normal serum plasma cholesterol and

30



spontaneous atherosclerotic lesions. This is similar to a disease in people who have a variant form of the apoE gene that is defective in binding to the LDL receptor and are at risk for early development of atherosclerosis and increased plasma triglyceride and cholesterol levels. There are indications that apoE is also involved in immune system regulation, nerve  
5 regeneration and muscle differentiation. The apoE knockout mice can be used to study the role of apoE in lipid metabolism, atherogenesis, and nerve injury, and to investigate intervention therapies that modify the atherogenic process.

*ApoE4 Targeted Replacement Mouse (Order Model #: 001549-M)* ApoE is a plasma protein involved in cholesterol transport, and the three human isoforms (E2, E3, and E4) have been  
10 associated with atherosclerosis and Alzheimer's disease. Gene targeting of 129 ES cells was used to replace the coding sequence of mouse apoE with human APOE4 without disturbing the murine regulatory sequences. The E4 isoform occurs in approximately 14% of the human population and is associated with increased plasma cholesterol and a greater risk of coronary artery disease. The Taconic apoE4 Targeted Replacement model has normal  
15 plasma cholesterol and triglyceride levels, but altered quantities of different plasma lipoprotein particles. This model also has delayed plasma clearance of cholesterol-rich lipoprotein particles (VLDL), with only half the clearance rate seen in the apoE3 Targeted Replacement model. Like the apoE3 model, the apoE4 mice develop altered plasma lipoprotein values and atherosclerotic plaques on an atherogenic diet. However, the  
20 atherosclerosis is more severe in the apoE4 model, with larger plaques and cholesterol apoE and apoB-48 levels twice that seen in the apoE3 model. The Taconic apoE4 Targeted Replacement model, along with the apoE2 and apoE3 Targeted Replacement Mice, provide an excellent tool for *in vivo* study of the human apoE isoforms.

*CETP Transgenic Mice (Order Model #: 1003-T)* These animals express the human plasma  
25 enzyme, CETP, resulting in mice with a dramatic reduction in serum HDL cholesterol. The mice can be useful in identifying and evaluating compounds that increase the levels of HDL cholesterol for reducing the risk of developing atherosclerosis

*Transgene/Promoter: human apolipoprotein A-I* These mice produce mouse HDL cholesterol particles that contain human apolipoprotein A-I. Transgenic expression is life-

long in both sexes (Biochemical Genetics and Metabolism Laboratory, Rockefeller University, NY City).

*A Mouse Model for Abetalipoproteinemia* Abetalipoproteinemia, an inherited human disease  
5 characterized by a near-complete absence of apoB-containing lipoproteins in the plasma, is  
caused by mutations in the gene for microsomal triglyceride transfer protein (MTP). Gene  
targeting was used to knock out the mouse MTP gene (*Mttp*). In heterozygous knockout  
mice (*Mttp*<sup>+/-</sup>), the MTP mRNA, protein, and activity levels were reduced by 50% in both  
liver and intestine. Recent studies with heterozygous MTP knockout mice have suggested  
10 that half-normal levels of MTP in the liver reduce apoB secretion. They hypothesized that  
reduced apoB secretion in the setting of half-normal MTP levels might be caused by a  
reduced MTP:apoB ratio in the endoplasmic reticulum, which would reduce the number of  
apoB-MTP interactions. If this hypothesis were true, half-normal levels of MTP might have  
little impact on lipoprotein secretion in the setting of half-normal levels of apoB synthesis  
15 (since the ratio of MTP to apoB would not be abnormally low) and might cause an  
exaggerated reduction in lipoprotein secretion in the setting of apoB overexpression (since  
the ratio of MTP to apoB would be even lower). To test this hypothesis, they examined the  
effects of heterozygous MTP deficiency on apoB metabolism in the setting of normal levels  
of apoB synthesis, half-normal levels of apoB synthesis (heterozygous *ApoB* deficiency), and  
20 increased levels of apoB synthesis (transgenic overexpression of human apoB). Contrary to  
their expectations, half-normal levels of MTP reduced plasma apoB-100 levels to the same  
extent (~25–35%) at each level of apoB synthesis. In addition, apoB secretion from primary  
hepatocytes was reduced to a comparable extent at each level of apoB synthesis. Thus, these  
results indicate that the concentration of MTP within the endoplasmic reticulum, rather than  
25 the MTP:apoB ratio, is the critical determinant of lipoprotein secretion. Finally,  
heterozygosity for an apoB knockout mutation was found to lower plasma apoB-100 levels  
more than heterozygosity for an MTP knockout allele. Consistent with that result, hepatic  
triglyceride accumulation was greater in heterozygous apoB knockout mice than in  
heterozygous MTP knockout mice. Cre/*loxP* tissue-specific recombination techniques were  
30 also used to generate liver-specific *Mttp* knockout mice. Inactivation of the *Mttp* gene in the  
liver caused a striking reduction in very low density lipoprotein (VLDL) triglycerides and

large reductions in both VLDL/low density lipoproteins (LDL) and high density lipoprotein cholesterol levels. Histologic studies in liver-specific knockout mice revealed moderate hepatic steatosis. Currently being tested is the hypothesis that accumulation of triglycerides in the liver renders the liver more susceptible to injury by a second insult (*e.g.*,  
5 lipopolysaccharide).

*Human apo B (apolipoprotein B) Transgene mice show apo B locus may have a causative role male infertility* The fertility of apoB (apolipoprotein B) (+/-) mice was recorded during the course of backcrossing (to C57BL/6J mice) and test mating. No apparent fertility problem was observed in female apoB (+/-) and wild-type female mice, as was documented  
10 by the presence of vaginal plugs in female mice. Although apoB (+/-) mice mated normally, only 40% of the animals from the second backcross generation produced any offspring within the 4-month test period. Of the animals that produced progeny, litters resulted from < 50% of documented matings. In contrast, all wild-type mice (6/6--*i.e.*, 100%) tested were fertile. These data suggest genetic influence on the infertility phenotype, as a small number  
15 of male heterozygotes were not sterile. Fertilization *in vivo* was dramatically impaired in male apoB (+/-) mice. 74% of eggs examined were fertilized by the sperm from wild-type mice, whereas only 3% of eggs examined were fertilized by the sperm from apoB (+/-) mice. The sperm counts of apoB (+/-) mice were mildly but significantly reduced compared with controls. However, the percentage of motile sperm was markedly reduced in the apoB (+/-)  
20 animals compared with that of the wild-type controls. Of the sperm from apoB (+/-) mice, 20% (*i.e.*, 4.9% of the initial 20% motile sperm) remained motile after 6 hr of incubation, whereas 45% (*i.e.*, 33.6% of the initial 69.5%) of the motile sperm retained motility in controls after this time. *In vitro* fertilization yielded no fertilized eggs in three attempts with apo B (+/-) mice, while wild-type controls showed a fertilization rate of 53%. However,  
25 sperm from apoB (+/-) mice fertilized 84% of eggs once the zona pellucida had been removed. Numerous sperm from apoB (+/-) mice were seen binding to zona-intact eggs. However, these sperm lost their motility when observed 4-6 hours after binding, showing that sperm from apoB (+/-) mice were unable to penetrate the zona pellucida but that the interaction between sperm and egg was probably not direct. Sperm binding to zona-free  
30 oocytes was abnormal. In the apoB (+/-) mice, sperm binding did not attenuate, even after

pronuclei had clearly formed, suggesting that apoB deficiency results in abnormal surface interaction between the sperm and egg.

Knockout of the mouse apoB gene resulted in embryonic lethality in homozygotes, protection against diet-induced hypercholesterolemia in heterozygotes, and developmental  
5 abnormalities in mice.

*Model of insulin resistance, dyslipidemia & overexpression of human apoB* It was shown that the livers of apoB mice assemble and secrete increased numbers of VLDL particles.

### **Example 3. Treatment of Diabetes Type-2 with iRNA**

10 *Introduction* The regulation of hepatic gluconeogenesis is an important process in the adjustment of the blood glucose level. Pathological changes in the glucose production of the liver are a central characteristic in type-2-diabetes. For example, the fasting hyperglycemia observed in patients with type-2-diabetes reflects the lack of inhibition of hepatic gluconeogenesis and glycogenolysis due to the underlying insulin resistance in this disease.  
15 Extreme conditions of insulin resistance can be observed for example in mice with a liver-specific insulin receptor knockout ('LIRKO'). These mice have an increased expression of the two rate-limiting gluconeogenic enzymes, phosphoenolpyruvate carboxykinase (PEPCK) and the glucose-6-phosphatase catalytic subunit (G6Pase). Insulin is known to repress both PEPCK and G6Pase gene expression at the transcriptional level and the signal transduction  
20 involved in the regulation of G6Pase and PEPCK gene expression by insulin is only partly understood. While PEPCK is involved in a very early step of hepatic gluconeogenesis (synthesis of phosphoenolpyruvate from oxaloacetate), G6Pase catalyzes the terminal step of both, gluconeogenesis and glycogenolysis, the cleavage of glucose-6-phosphate into phosphate and free glucose, which is then delivered into the blood stream.

25 The pharmacological intervention in the regulation of expression of PEPCK and G6Pase can be used for the treatment of the metabolic aberrations associated with diabetes. Hepatic glucose production can be reduced by an iRNA-based reduction of PEPCK and G6Pase enzymatic activity in subjects with type-2-diabetes.

Targets for iRNA

**Glucose-6-phosphatase (G6Pase)**

G6Pase mRNA is expressed principally in liver and kidney, and in lower amounts in the small intestine. Membrane-bound G6Pase is associated with the endoplasmic reticulum.

5 Low activities have been detected in skeletal muscle and in astrocytes as well.

G6Pase catalyzes the terminal step in gluconeogenesis and glycogenolysis. The activity of the enzyme is several fold higher in diabetic animals and probably in diabetic humans. Starvation and diabetes cause a 2-3-fold increase in G6Pase activity in the liver and a 2-4-fold increase in G6Pase mRNA.

10

**Phosphoenolpyruvate carboxykinase (PEPCK)**

Overexpression of PEPCK in mice results in symptoms of type-2-diabetes mellitus. PEPCK overexpression results in a metabolic pattern that increases G6Pase mRNA and results in a selective decrease in insulin receptor substrate (IRS)-2 protein, decreased  
15 phosphatidylinositol 3-kinase activity, and reduced ability of insulin to suppress gluconeogenic gene expression.

**Table 7. Other targets to inhibit hepatic glucose production**

Target	Comment
FKHR	good evidence for antidiabetic phenotype (Nakae <i>et al.</i> , <i>Nat Genetics</i> 32:245(2002))
Glucagon	
Glucagon receptor	
Glycogen phosphorylase	
PGC-1 (PPAR-Gamma Coactivator)	regulates the cAMP response (and probably the PKB/FKHR-regulation) on PEPCK/G6Pase
Fructose-1,6-bisphosphatase	
Glucose-6-phospate translocator	
Glucokinase inhibitory regulatory protein	

20

**Materials and Methods**

Animals: BKS.Cg-m +/- Lepr db mice, which contain a point mutation in the leptin receptor gene are used to examine the efficacy of iRNA for the targets listed above.



BKS.Cg-m +/- Lepr db are available from the Jackson Laboratory (Stock Number 000642). These animals are obese at 3-4 weeks after birth, show elevation of plasma insulin at 10 to 14 days, elevation of blood sugar at 4 to 8 weeks, and uncontrolled rise in blood sugar. Exogenous insulin fails to control blood glucose levels and gluconeogenic activity increases.

The following numbers of male animals (age>12 weeks) would ideally be tested with the following iRNAs:

PEPCK, 2 sequences, 5 animals per sequence  
G6Pase, 2 sequences, 5 animals per sequence  
1 nonspecific sequence, 5 animals  
1 control group (only injected, no siRNA), 5 animals  
1 control group (not injected, no siRNA), 5 animals

Reagents: Necessary reagents would ideally include a Glucometer Elite XL (Bayer, Pittsburgh, PA) for glucose quantification, and an Insulin Radioimmunoassay (RIA) kit (Amersham, Piscataway, NJ) for insulin quantitation

#### Assays:

G6P enzyme assays and PEPCK enzyme assays are used to measure the activity of the enzymes. Northern blotting is used to detect levels of G6Pase and PEPCK mRNA. Antibody-based techniques (*e.g.*, immunoblotting, immunofluorescence) are used to detect levels of G6Pase and PEPCK protein. Glycogen staining is used to detect levels of glycogen in the liver. Histological analysis is performed to analyze tissues.

#### Gene information:

**G6Pase** GenBank® No.: NM\_008061, Mus musculus glucose-6-phosphatase, catalytic (G6pc), mRNA 1..2259, ORF 83..1156;  
GenBank® No: U00445, Mus musculus glucose-6-phosphatase mRNA, complete cds 1..2259, ORF 83..1156  
GenBank® No: BC013448  
**PEPCK**

GenBank® No: NM\_011044, Mus musculus phosphoenolpyruvate carboxykinase 1, cytosolic (Pck1), mRNA.1..2618, ORF 141..2009  
GenBank® No: AF009605.1

5 Administration of iRNA:

iRNA corresponding to the genes described above would be administered to mice with hydrodynamic injection. One control group of animals would be treated with Metformin as a positive control for reduction in hepatic glucose levels.

10 **Experimental Protocol**

Mice would be housed in a facility in which there is light from 7:00 AM to 7:00 PM. Mice would be fed *ad libidum* from 7:00 PM to 7:00 AM and fast from 7:00 AM to 7:00 PM.

**Day 0:** 7:00 PM: Approximately 100 µl blood would be drawn from the tail. Serum would be isolated to measure glucose, insulin, HbA1c (EDTA-blood), glucagon, FFAs, lactate,  
15 corticosterone, serum triglycerides.

**Day 1-7:** Blood glucose would be measured daily at 8:00 AM and 6:00 PM (approx. 3-5 µl; measured with a Haemoglucometer)

**Day 8:** Blood glucose would be measured daily at 8:00 AM and 6:00 PM. iRNA would be injected between 10:00 AM and 2:00 PM

20

**Day 9-20:** Blood glucose would be measured daily at 8:00 AM and 6:00 PM.

**Day 21:** Mice would be sacrificed after 10 hours of fasting.

Blood would be isolated. Glucose, insulin, HbA1c (EDTA-blood), glucagon, FFAs, lactate,  
25 corticosterone, serum triglycerides would be measured. Liver tissue would be isolated for histology, protein assays, RNA assays, glycogen quantitation, and enzyme assays.

**Example 4: Inhibition of Glucose-6-Phosphatase iRNA *in vivo***

iRNA targeted to the Glucose-6-Phosphatase (G6P) gene was used to examine the effects of inhibition of G6P expression on glucose metabolism *in vivo*.

5 Female mice, 10 weeks of age, strain BKS.Cg-m +/- Lepr db (The Jackson Laboratory) were used for *in vivo* analysis of enzymes of the hepatic glucose production. Mice were housed under conditions where it was light from 6:30 am to 6:30 pm. Mice were fed (ad libidum) during the night period and fasted during the day period.

On day 1, approximately 100µl of blood was collected from test animals by puncturing the  
10 retroorbital plexus. On days 1-7, blood glucose was measured in blood obtained from tail veins (approximately 3-5 µl) using a Glucometer (Elite XL, Bayer). Blood glucose was sampled daily at 8 am and 6 pm.

On day 7 at approximately 2pm, GL3 plasmid (10 µg) and siRNAs (100 µg G6Pase specific, Renilla nonspecific or no siRNA control) were delivered to animals using  
15 hydrodynamic coinjection.

On day 8, GL3 expression was analyzed by injection of luciferin (3 mg) after anaesthesia with avertin and imaging. This was done to control for successful hydrodynamic delivery.

On days 8-10, blood glucose was measured in blood obtained from tail veins  
20 (approximately 3-5 µl) using a Glucometer (Elite XL, Bayer).

On day 10, mice were sacrificed after 10 hours of fasting. Blood and liver were isolated from sacrificed animals.

Results: Coinjection of GL3 plasmid and G6Pase iRNA (G6P4) reduced blood glucose levels for the short term. Coinjection of GL3 plasmid and Renilla nonspecific iRNA  
25 had no effect on blood glucose levels.

**Example 5: Selected Palindromic Sequences**

Tables 8-13 below provide selected palindromic sequences from the following genes: human ApoB, human glucose-6-phosphatase, rat glucose-6-phosphatase,  $\beta$ -catenin, and hepatitis C virus (HCV).

5

Table 8. Selected palindromic sequences from human ApoB

	Source	Start Index	End Index		Match	Start Index	End Index	#	B
SEQ ID NO: 1	ggccattccagaaggggaag	509	528	SEQ ID NO: 1004	cttccgttctgtaatggcc	5795	5814	1	9
SEQ ID NO: 2	tgccatctcgagagttcca	4099	4118	SEQ ID NO: 1005	tggaaactctctccatggca	10876	10895	1	8
SEQ ID NO: 3	catgtcaaacaactttgtta	7056	7075	SEQ ID NO: 1006	taacaaattccttgacatg	7358	7377	1	8
SEQ ID NO: 4	tttgtataaatcttattg	7068	7087	SEQ ID NO: 1007	caataagatcaatagcaaa	8990	9009	1	8
SEQ ID NO: 5	tctggaaaagggcatgga	8880	8899	SEQ ID NO: 1008	tccatgtlcccatctacaga	11356	11375	1	8
SEQ ID NO: 6	cagctctgttcagggtcca	10900	10919	SEQ ID NO: 1009	tggacctgcaccaaagctg	13952	13971	1	8
SEQ ID NO: 7	ggagggtccccagctctgc	356	375	SEQ ID NO: 1010	gcagccctgggaaaactcc	6447	6466	1	7
SEQ ID NO: 8	ctgttttgaagactctcca	1081	1100	SEQ ID NO: 1011	tggagggttagtcataacag	10327	10346	1	7
SEQ ID NO: 9	agtggctgaaacgtgtgca	1297	1316	SEQ ID NO: 1012	tgcagagcttctgccact	13508	13527	1	7
SEQ ID NO: 10	ccaaaatagaaggggaatct	2068	2087	SEQ ID NO: 1013	agattcctttgccttttg	4000	4019	1	7
SEQ ID NO: 11	tgaagagaagattgaattt	3620	3639	SEQ ID NO: 1014	aaattctctttcttttca	9212	9231	1	7
SEQ ID NO: 12	agtgttggaacaccagca	4230	4249	SEQ ID NO: 1015	tgctagtgaggccaacact	10649	10668	1	7
SEQ ID NO: 13	aaggctccacaagtcacat	5950	5969	SEQ ID NO: 1016	tgatgatatctggaacctt	10724	10743	1	7
SEQ ID NO: 14	gtcagccagggttatagca	7725	7744	SEQ ID NO: 1017	tgctaagaaccttactgac	7781	7800	1	7
SEQ ID NO: 15	tgatatctggaaccttgaa	10727	10746	SEQ ID NO: 1018	ttcactgttcctgaaatca	7863	7882	1	7
SEQ ID NO: 16	gtcaagttgagcaatttct	13423	13442	SEQ ID NO: 1019	agaaaaggcacaccttgac	11072	11091	1	7
SEQ ID NO: 17	atccagatggaaaaggga	13480	13499	SEQ ID NO: 1020	ttccaattccctgtggat	3680	3699	1	7
SEQ ID NO: 18	attgtttgtcaaagaagt	4543	4562	SEQ ID NO: 1021	acttcagagaaatacaaat	11401	11420	4	6
SEQ ID NO: 19	ctggaaaatgtcagcctgg	204	223	SEQ ID NO: 1022	ccagacttccgtttaccag	8235	8254	2	6
SEQ ID NO: 20	accaggaggttcttcttca	1729	1748	SEQ ID NO: 1023	tgaagtgtagtctctctggt	5089	5108	2	6
SEQ ID NO: 21	aaagaagtctgaaagaat	1956	1975	SEQ ID NO: 1024	attccatcacaaatccttt	9661	9680	2	6
SEQ ID NO: 22	gctacagcttatggctcca	3570	3589	SEQ ID NO: 1025	tggatctaaatgcagtagc	11623	11642	2	6
SEQ ID NO: 23	atcaatattgatcaatttg	6414	6433	SEQ ID NO: 1026	caaagaagtcaagattgat	4553	4572	2	6
SEQ ID NO: 24	gaattatcttttaaaacat	7326	7345	SEQ ID NO: 1027	atgtgttaacaaaatattc	11494	11513	2	6
SEQ ID NO: 25	cgaggcccgctgctggc	130	149	SEQ ID NO: 1028	gccagaagtgcagatcctcg	3507	3526	1	6
SEQ ID NO: 26	acaactatgaggctgagag	271	290	SEQ ID NO: 1029	ctctgagcaacaaatttgt	10309	10328	1	6
SEQ ID NO: 27	gctgagagttccagtggag	282	301	SEQ ID NO: 1030	ctccatggcaaatgtcagc	10885	10904	1	6
SEQ ID NO: 28	tgaagaaaaccaagaactc	448	467	SEQ ID NO: 1031	gagtcattgaggttcttca	4929	4948	1	6
SEQ ID NO: 29	cctacttacatcctgaaca	558	577	SEQ ID NO: 1032	tggtcataaggaggtagg	12766	12785	1	6
SEQ ID NO: 30	ctacttacatcctgaacat	559	578	SEQ ID NO: 1033	atgttcataaggaggttag	12765	12784	1	6
SEQ ID NO: 31	gagacagaagaagccaagc	615	634	SEQ ID NO: 1034	gcttggtttgccagtctc	2459	2478	1	6
SEQ ID NO: 32	cactcactttaccgtcaag	671	690	SEQ ID NO: 1035	cttgaacacaaagtcagtg	6000	6019	1	6
SEQ ID NO: 33	ctgatcagcagcagccagt	822	841	SEQ ID NO: 1036	actgggaagtgccttatcag	5237	5256	1	6
SEQ ID NO: 34	actggacgctaagaggaag	854	873	SEQ ID NO: 1037	cttcccaaaagagaccagt	2890	2909	1	6



SEQ ID NO: 35	agaggaagcatgtggcaga	865	884	SEQ ID NO: 1038	tctggcatttactttctct	5921	5940	1	6
SEQ ID NO: 36	tgaagactctccaggaact	1087	1106	SEQ ID NO: 1039	agttgaaggagactatica	7216	7235	1	6
SEQ ID NO: 37	ctctgagcaaaatatccag	1121	1140	SEQ ID NO: 1040	ctggttactgagctgagag	1161	1180	1	6
SEQ ID NO: 38	atgaagcagtcacatctct	1189	1208	SEQ ID NO: 1041	agagctgccagtccttcat	10016	10035	1	6
SEQ ID NO: 39	ttgccacagctgattgagg	1209	1228	SEQ ID NO: 1042	cctcctacagtggtggcaa	4222	4241	1	6
SEQ ID NO: 40	agctgattgaggtgtccag	1216	1235	SEQ ID NO: 1043	ctggattccacatgcagct	11847	11866	1	6
SEQ ID NO: 41	tgtccactcacatcctcc	1278	1297	SEQ ID NO: 1044	ggagggtttaagttcagca	7601	7620	1	6
SEQ ID NO: 42	tgaacgtgtgcatgccaa	1303	1322	SEQ ID NO: 1045	ttgggagagacaagttica	6500	6519	1	6
SEQ ID NO: 43	gacattgctaattacctga	1503	1522	SEQ ID NO: 1046	tcagaagctaagcaatgtc	7232	7251	1	6
SEQ ID NO: 44	ttcttctcagactttcct	1738	1757	SEQ ID NO: 1047	aggagagtccaaattagaa	8498	8517	1	6
SEQ ID NO: 45	ccaatatcttgaactcaga	1903	1922	SEQ ID NO: 1048	tctgaattcattcaattgg	6485	6504	1	6
SEQ ID NO: 46	aaagttagtgaagaagtt	1946	1965	SEQ ID NO: 1049	aactaccctcactgccttt	2132	2151	1	6
SEQ ID NO: 47	aagttagtgaagaagttc	1947	1966	SEQ ID NO: 1050	gaacctctggcatttactt	5916	5935	1	6
SEQ ID NO: 48	aaagaagttctgaaagaat	1956	1975	SEQ ID NO: 1051	attctctggttaactacttt	5482	5501	1	6
SEQ ID NO: 49	tttggtataccaaagatg	2322	2341	SEQ ID NO: 1052	catcttaggcactgacaaa	4997	5016	1	6
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SEQ ID NO: 51	caggaagggctcaaagaat	2561	2580	SEQ ID NO: 1054	attcctttaacaattcctg	9492	9511	1	6
SEQ ID NO: 52	aggaagggctcaaagaatg	2562	2581	SEQ ID NO: 1055	cattcctttaacaattcct	9491	9510	1	6
SEQ ID NO: 53	gaagggctcaaagaatgac	2564	2583	SEQ ID NO: 1056	gtcagctctcaggctcttc	7914	7933	1	6
SEQ ID NO: 54	caaagaatgactttttct	2572	2591	SEQ ID NO: 1057	agaaggatggcattttttg	14000	14019	1	6
SEQ ID NO: 55	catggagaatgcctttgaa	2603	2622	SEQ ID NO: 1058	ttcagagccaaagtccatg	7119	7138	1	6
SEQ ID NO: 56	ggagccaaggctggagtaa	2679	2698	SEQ ID NO: 1059	ttactccaacgccagctcc	3050	3069	1	6
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SEQ ID NO: 58	acctatgagctccagagag	3165	3184	SEQ ID NO: 1061	ctctcaagaccacagaggt	12976	12995	1	6
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SEQ ID NO: 60	accctggacattcagaaca	3387	3406	SEQ ID NO: 1063	tgttgctaagggtcagggt	5675	5694	1	6
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SEQ ID NO: 62	gatgaagagaagattgaat	3618	3637	SEQ ID NO: 1065	attccagcttccccacatc	8330	8349	1	6
SEQ ID NO: 63	caatgtagataccaaaaaa	3656	3675	SEQ ID NO: 1066	tttttggaatgccattg	8643	8662	1	6
SEQ ID NO: 64	gtagataccaaaaaaatga	3660	3679	SEQ ID NO: 1067	tcattgtatgggtctctac	4371	4390	1	6
SEQ ID NO: 65	gcctcagttcatttgact	4509	4528	SEQ ID NO: 1068	agtcaagaaggacttaagc	5304	5323	1	6
SEQ ID NO: 66	ttgtttgtcaaagaagtc	4544	4563	SEQ ID NO: 1069	gacttcagagaaatacaaa	11400	11419	1	6
SEQ ID NO: 67	ttgtttgtcaaagaagtca	4545	4564	SEQ ID NO: 1070	tgacttcagagaaatacaa	11399	11418	1	6
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SEQ ID NO: 71	aaagtcagtgccctgctta	6009	6028	SEQ ID NO: 1074	taagaaccttactgacttt	7784	7803	1	6

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SEQ ID NO: 74	taaagatagttatgattta	6665	6684	SEQ ID NO: 1077	taaaccaaaacttggttta	9019	9038	1	6
SEQ ID NO: 75	tattgatgaaatcattgaa	6713	6732	SEQ ID NO: 1078	ttcaaagacttaaaaaata	8007	8026	1	6
SEQ ID NO: 76	atgatctacatttgtttat	6790	6809	SEQ ID NO: 1079	ataaagaaattaaagtcac	7380	7399	1	6
SEQ ID NO: 77	agagacacatacagaatat	6919	6938	SEQ ID NO: 1080	atatattgtcagtgccctct	13382	13401	1	6
SEQ ID NO: 78	gacacatacagaataataga	6922	6941	SEQ ID NO: 1081	tctaaattcagttcttgctc	11327	11346	1	6
SEQ ID NO: 79	agcatgtcaaacactttgt	7054	7073	SEQ ID NO: 1082	acaaagtcagtgccctgct	6007	6026	1	6
SEQ ID NO: 80	tttttagaggaaaccaagg	7515	7534	SEQ ID NO: 1083	cctttgtgtacaccaaaaa	11230	11249	1	6
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SEQ ID NO: 82	ggaagatagacttcctgaa	9307	9326	SEQ ID NO: 1085	ttcagaaatactgttttcc	12824	12843	1	6
SEQ ID NO: 83	cactgtttctgagtcccag	9334	9353	SEQ ID NO: 1086	ctgggacctaccaagagtg	12523	12542	1	6
SEQ ID NO: 84	cacaaatcctttggctgtg	9668	9687	SEQ ID NO: 1087	cacatttcaagggaattgtg	10063	10082	1	6
SEQ ID NO: 85	ttcctggatacactgttcc	9853	9872	SEQ ID NO: 1088	ggaactgttgactcaggaa	12569	12588	1	6
SEQ ID NO: 86	gaaatctcaagctttctct	10042	10061	SEQ ID NO: 1089	agagccaggctcagcttcc	11044	11063	1	6
SEQ ID NO: 87	tttctcatcttcatctgt	10210	10229	SEQ ID NO: 1090	acagctgaaagagatgaaa	13055	13074	1	6
SEQ ID NO: 88	tctaccgctaaaggagcag	10521	10540	SEQ ID NO: 1091	ctgcacgctttgaggtaga	11761	11780	1	6
SEQ ID NO: 89	ctaccgctaaaggagcagt	10522	10541	SEQ ID NO: 1092	actgcacgctttgaggtag	11760	11779	1	6
SEQ ID NO: 90	agggcctcttttcaccaa	10831	10850	SEQ ID NO: 1093	ttggccagggaagtggccct	10957	10976	1	6
SEQ ID NO: 91	ttctccatccctgtaaaag	11265	11284	SEQ ID NO: 1094	cttttcaccaacggagaa	10838	10857	1	6
SEQ ID NO: 92	gaaaaacaaagcagattat	11816	11835	SEQ ID NO: 1095	ataaactgcaagatttttc	13600	13619	1	6
SEQ ID NO: 93	actcactcattgattttct	12682	12701	SEQ ID NO: 1096	agaaaatcaggatctgagt	14027	14046	1	6
SEQ ID NO: 94	taactaatagatgtaatc	12890	12909	SEQ ID NO: 1097	gattaccaccagcagttta	13578	13597	1	6
SEQ ID NO: 95	caaaacgagcttcaggaag	13200	13219	SEQ ID NO: 1098	cttcgtgaagaalatatttg	13260	13279	1	6
SEQ ID NO: 96	tggaataatgctcagtggt	2366	2385	SEQ ID NO: 1099	aacacttacttgaattcca	10662	10681	3	5
SEQ ID NO: 97	gatttgaaatccaaagaag	2400	2419	SEQ ID NO: 1100	cttcagagaaatacaaatc	11402	11421	3	5
SEQ ID NO: 98	atttgaaatccaaagaagt	2401	2420	SEQ ID NO: 1101	acttcagagaaatacaaat	11401	11420	3	5
SEQ ID NO: 99	atcaacagccgcttctttg	990	1009	SEQ ID NO: 1102	caaagaagtcaagattgat	4553	4572	2	5
SEQ ID NO: 100	tgttttgaagactctccag	1082	1101	SEQ ID NO: 1103	ctggaaagttaaaacaaca	6955	6974	2	5
SEQ ID NO: 101	cccttctgatagatgtggt	1324	1343	SEQ ID NO: 1104	accaaagctggcaccaggg	13961	13980	2	5
SEQ ID NO: 102	tgagcaagtgaagaacttt	1868	1887	SEQ ID NO: 1105	aaagccattcagttctctca	12963	12982	2	5
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SEQ ID NO: 104	atccaaagaagtcccggaa	2408	2427	SEQ ID NO: 1107	ttccggggaaacctgggat	12721	12740	2	5
SEQ ID NO: 105	agagcctacctccgcatct	2430	2449	SEQ ID NO: 1108	agatggtacgttagcctct	11921	11940	2	5
SEQ ID NO: 106	aatgcctttgaactcccca	2610	2629	SEQ ID NO: 1109	tgggaaactacaatttcatt	7012	7031	2	5
SEQ ID NO: 107	gaagtccaaattccggatt	3297	3316	SEQ ID NO: 1110	aatcttcaatttattcttc	13815	13834	2	5
SEQ ID NO: 108	tgcaagcagaagccagaag	3496	3515	SEQ ID NO: 1111	cttcagggttccatcgtgca	11376	11395	2	5
SEQ ID NO: 109	gaagagaagattgaatttg	3621	3640	SEQ ID NO: 1112	caaaacctactgtctcttc	10459	10478	2	5

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SEQ ID NO: 113	aggagcctacccaaaataat	5594	5613	SEQ ID NO: 1116	attatgttgaaacagtcct	11830	11849	2	5
SEQ ID NO: 114	aaagctgaagcacatcaat	6401	6420	SEQ ID NO: 1117	attgttgctcatctcctt	10194	10213	2	5
SEQ ID NO: 115	ctgctggaaacaacgagaa	9418	9437	SEQ ID NO: 1118	ttctgattaccaccagcag	13574	13593	2	5
SEQ ID NO: 116	ttgaaggaattcttgaaaa	9582	9601	SEQ ID NO: 1119	ttttaaagaaatcttcaa	13805	13824	2	5
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SEQ ID NO: 122	ctgcgctgctgctgctgct	154	173	SEQ ID NO: 1125	agcagaagggtgcgaagcag	3224	3243	1	5
SEQ ID NO: 123	gctgctggcgggcccagg	170	189	SEQ ID NO: 1126	cctggattccacatgcagc	11846	11865	1	5
SEQ ID NO: 124	aagaggaaatgctggaaaa	193	212	SEQ ID NO: 1127	ttttcttactacatctt	2584	2603	1	5
SEQ ID NO: 125	ctggaaaatgtcagcctgg	204	223	SEQ ID NO: 1128	ccagacttccacatcccag	3915	3934	1	5
SEQ ID NO: 126	tggagtccctgggactgct	296	315	SEQ ID NO: 1129	agcatgcctagttctcca	9945	9964	1	5
SEQ ID NO: 127	ggagtccctgggactgctg	297	316	SEQ ID NO: 1130	cagcatgcctagttctcc	9944	9963	1	5
SEQ ID NO: 128	tgggactgctgattcaaga	305	324	SEQ ID NO: 1131	tcttccatcacttgacca	2042	2061	1	5
SEQ ID NO: 129	ctgctgattcaagaagtgc	310	329	SEQ ID NO: 1132	gcacaccttgacattgcag	11079	11098	1	5
SEQ ID NO: 130	tgccaccaggatcaactgc	326	345	SEQ ID NO: 1133	gcaggctgaactggtggca	2717	2736	1	5
SEQ ID NO: 131	gccaccaggatcaactgca	327	346	SEQ ID NO: 1134	tgcaggctgaactggtggc	2716	2735	1	5
SEQ ID NO: 132	tgcaagggtgagctggagg	342	361	SEQ ID NO: 1135	cctccacctctgatctgca	4744	4763	1	5
SEQ ID NO: 133	caagggtgagctggaggtt	344	363	SEQ ID NO: 1136	aaccttcatatgaagcttg	13755	13774	1	5
SEQ ID NO: 134	ctctgcagcttcatctga	369	388	SEQ ID NO: 1137	tcaggaagcttctcaagag	13211	13230	1	5
SEQ ID NO: 135	cagcttcatctgaagacc	374	393	SEQ ID NO: 1138	ggtcttgagttaaatgctg	4977	4996	1	5
SEQ ID NO: 136	gcttcatctgaagaccag	376	395	SEQ ID NO: 1139	ctggacgctaagaggaagc	855	874	1	5
SEQ ID NO: 137	tcatctgaagaccagcca	379	398	SEQ ID NO: 1140	tggcatggcattatgatga	3604	3623	1	5
SEQ ID NO: 138	gaaaaccaagaactctgag	452	471	SEQ ID NO: 1141	ctcaaccttaatgatttc	8286	8305	1	5
SEQ ID NO: 139	agaactctgaggagtttgc	460	479	SEQ ID NO: 1142	gcaagctatacagtattct	8377	8396	1	5
SEQ ID NO: 140	tctgaggagittgctgcag	465	484	SEQ ID NO: 1143	ctgcaggggatccccaga	2526	2545	1	5
SEQ ID NO: 141	tttgctgcagccatgtcca	474	493	SEQ ID NO: 1144	tggaaagtgtcagtgga	10372	10391	1	5
SEQ ID NO: 142	caagaggggcatcattct	578	597	SEQ ID NO: 1145	agaataaatgacgttcttg	7035	7054	1	5
SEQ ID NO: 143	tcactttaccgtcaagacg	674	693	SEQ ID NO: 1146	cgtctacactatcatgtga	4360	4379	1	5
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SEQ ID NO: 145	cactggacgctaagaggaa	853	872	SEQ ID NO: 1148	ttccagaaagcagccagtg	12498	12517	1	5
SEQ ID NO: 146	aggaagcatgtggcagaag	867	886	SEQ ID NO: 1149	cttcatacacattaatcct	9988	10007	1	5
SEQ ID NO: 147	caaggagcaacacctcttc	893	912	SEQ ID NO: 1150	gaagiagtactgcacttg	6835	6854	1	5



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SEQ ID NO: 150	agcagtcacatctctcttg	1193	1212	SEQ ID NO: 1153	caaggagaaactgactgct	6524	6543	1	5
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SEQ ID NO: 156	ccacctgtatgcgctgag	1429	1448	SEQ ID NO: 1159	ctcagggatctgaagggtgg	8187	8206	1	5
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SEQ ID NO: 159	ggacattgctaattacctg	1502	1521	SEQ ID NO: 1162	caggatatattcgaaagtcc	12798	12817	1	5
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SEQ ID NO: 162	agtcttcaatcctgaaatg	1630	1649	SEQ ID NO: 1165	catttctgattgggtggact	7757	7776	1	5
SEQ ID NO: 163	tgagcaagtgaagaacttt	1868	1887	SEQ ID NO: 1166	aaagtgccacttttactca	6183	6202	1	5
SEQ ID NO: 164	agcaagtgaagaactttgt	1870	1889	SEQ ID NO: 1167	acaaagtcagtgccctgct	6007	6026	1	5
SEQ ID NO: 165	tctgaaagaatctcaactt	1964	1983	SEQ ID NO: 1168	aagtccataatgggtcaga	12811	12830	1	5
SEQ ID NO: 166	actgtcatggacttcagaa	1986	2005	SEQ ID NO: 1169	ttctgaatatattgtcagt	13376	13395	1	5
SEQ ID NO: 167	acttgaccagcctcagcc	2051	2070	SEQ ID NO: 1170	ggctcaccctgagagaagt	12391	12410	1	5
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SEQ ID NO: 169	actacctcactgcctttg	2133	2152	SEQ ID NO: 1172	caaatttgtggagggtagt	10319	10338	1	5
SEQ ID NO: 170	ttggatttgcttcagctga	2149	2168	SEQ ID NO: 1173	tcagtataagtacaaccaa	9392	9411	1	5
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SEQ ID NO: 174	agacagtgtcaacaaagct	2246	2265	SEQ ID NO: 1177	agcttggtttgccagctct	2458	2477	1	5
SEQ ID NO: 175	ctttggctataccaaagat	2321	2340	SEQ ID NO: 1178	atctcgtgtctaggaaaag	5968	5987	1	5
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SEQ ID NO: 177	gatatggtaaataaataa	2355	2374	SEQ ID NO: 1180	ttatcttattaattatctc	13079	13098	1	5
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SEQ ID NO: 181	cagatgattggagaggtca	2541	2560	SEQ ID NO: 1184	tgaccacacaaacagtctg	5363	5382	1	5
SEQ ID NO: 182	agaatgactttttcttca	2575	2594	SEQ ID NO: 1185	tgaagtcoggattcattct	11015	11034	1	5
SEQ ID NO: 183	gaactccccactggagctg	2619	2638	SEQ ID NO: 1186	cagctcaaccgtacagttc	11861	11880	1	5
SEQ ID NO: 184	atatcttcatctggagtca	2652	2671	SEQ ID NO: 1187	tgacttcagtgcagaatat	11966	11985	1	5
SEQ ID NO: 185	gtcatgtctcccgagcca	2667	2686	SEQ ID NO: 1188	tggccccgtttaccatgac	5809	5828	1	5

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SEQ ID NO: 188	ctcattgagaacaggcagt	2976	2995	SEQ ID NO: 1191	actgactgcacgctttgag	11756	11775	1	5
SEQ ID NO: 189	ttgagcagtattctgtcag	3142	3161	SEQ ID NO: 1192	ctgagagaagtgtcttcaa	12399	12418	1	5
SEQ ID NO: 190	accttgccagtggaagtc	3285	3304	SEQ ID NO: 1193	ggacgggtactgtcccaggt	12784	12803	1	5
SEQ ID NO: 191	ccagtggaagtcacaattcc	3292	3311	SEQ ID NO: 1194	ggaaggcagagtttactgg	9148	9167	1	5
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SEQ ID NO: 199	acttccaatttccctgtgg	3678	3697	SEQ ID NO: 1202	ccacgaaaaatatggaagt	10360	10379	1	5
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SEQ ID NO: 203	acttccacatcccagaaaa	3919	3938	SEQ ID NO: 1206	ttttaacaaaagtgggaagt	6821	6840	1	5
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SEQ ID NO: 205	aaaagcgatggccgggtca	3948	3967	SEQ ID NO: 1208	tgactcactcattgatttt	12680	12699	1	5
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SEQ ID NO: 208	aagtcctacttttaccat	4117	4136	SEQ ID NO: 1211	atgggaagtataagaactt	4834	4853	1	5
SEQ ID NO: 209	tgctctctctgggtgtct	4159	4178	SEQ ID NO: 1212	agaaaaacaaacacaggca	9643	9662	1	5
SEQ ID NO: 210	accagcacagaccatttca	4242	4261	SEQ ID NO: 1213	tgaagtgtagtctcctggt	5089	5108	1	5
SEQ ID NO: 211	ccagcacagaccatttcag	4243	4262	SEQ ID NO: 1214	ctgaaatacaatgctctgg	5511	5530	1	5
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SEQ ID NO: 221	ttcttcagcctgtcttctg	4941	4960	SEQ ID NO: 1224	cagaatccagatacaagaa	6884	6903	1	5
SEQ ID NO: 222	ctggatcactaaattccca	4957	4976	SEQ ID NO: 1225	tgggtcttccagagccag	11033	11052	1	5
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SEQ ID NO: 224	agtgaacgaccaactga	5073	5092	SEQ ID NO: 1227	tcaaattcctggatacact	9848	9867	1	5
SEQ ID NO: 225	ctgggaagtgcctatcagg	5238	5257	SEQ ID NO: 1228	cctgaccttcacataccag	8310	8329	1	5
SEQ ID NO: 226	gcaaaaacattttcaactt	5278	5297	SEQ ID NO: 1229	aagtaaaagaaaatttgc	10744	10763	1	5
SEQ ID NO: 227	aaaaacattttcaacttca	5280	5299	SEQ ID NO: 1230	tgaagtaaaagaaaatttt	10742	10761	1	5
SEQ ID NO: 228	tcagtcaagaaggacttaa	5302	5321	SEQ ID NO: 1231	ttaaggacttccattctga	13363	13382	1	5
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SEQ ID NO: 230	cacacaaacagtcctgaaca	5367	5386	SEQ ID NO: 1233	tgtttcaactgcctttgtg	11219	11238	1	5
SEQ ID NO: 231	tcttcaaaacttgacaaca	5409	5428	SEQ ID NO: 1234	tgttttcctatttccaaga	12835	12854	1	5
SEQ ID NO: 232	caagttttataagcaaact	5441	5460	SEQ ID NO: 1235	agttattttgctaaacttg	14043	14062	1	5
SEQ ID NO: 233	tggtaactactttaaacag	5488	5507	SEQ ID NO: 1236	ctgttttttagaggaaacca	7512	7531	1	5
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SEQ ID NO: 236	aacacatctatgccatctc	5620	5639	SEQ ID NO: 1239	gagacagcatcttctgtgtt	11204	11223	1	5
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SEQ ID NO: 238	gcagacactgttgctaagg	5667	5686	SEQ ID NO: 1241	cctttcaagcactgactgc	11746	11765	1	5
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SEQ ID NO: 244	cttttactcagtgagccca	6192	6211	SEQ ID NO: 1247	tgggctaaacgtatgaaag	7827	7846	1	5
SEQ ID NO: 245	tcattgatgcttttagagat	6217	6236	SEQ ID NO: 1248	atcttcataagttcaatga	13174	13193	1	5
SEQ ID NO: 246	aaaaccaagatgttcactc	6295	6314	SEQ ID NO: 1249	gagtgaaatgctgtttttt	8630	8649	1	5
SEQ ID NO: 247	aggaatcgacaaaccatta	6357	6376	SEQ ID NO: 1250	taatgattttcaagttcct	8294	8313	1	5
SEQ ID NO: 248	tagttgtactggaaaacgt	6376	6395	SEQ ID NO: 1251	acgttagcctctaagacta	11928	11947	1	5
SEQ ID NO: 249	ggaaaacgtacagagaaag	6386	6405	SEQ ID NO: 1252	cttttacaattcattttcc	13014	13033	1	5
SEQ ID NO: 250	gaaaacgtacagagaaagc	6387	6406	SEQ ID NO: 1253	gctttctcttccacatttc	10052	10071	1	5
SEQ ID NO: 251	aaagctgaagcacatcaat	6401	6420	SEQ ID NO: 1254	attgaigttagagtgcctt	6984	7003	1	5
SEQ ID NO: 252	aagctgaagcacatcaata	6402	6421	SEQ ID NO: 1255	tattgatgttagagtgcctt	6983	7002	1	5
SEQ ID NO: 253	tgaagcacatcaatattga	6406	6425	SEQ ID NO: 1256	tcaaccttaatgattttca	8287	8306	1	5
SEQ ID NO: 254	atcaatattgatcaatttg	6414	6433	SEQ ID NO: 1257	caaagccatcactgatgat	1660	1679	1	5
SEQ ID NO: 255	taatgattatctgaattca	6476	6495	SEQ ID NO: 1258	tgaaatcattgaaaaatta	6719	6738	1	5
SEQ ID NO: 256	gattatctgaattcatica	6480	6499	SEQ ID NO: 1259	tgaagtagctgagaaaatc	7094	7113	1	5
SEQ ID NO: 257	aattgggagagacaagttt	6498	6517	SEQ ID NO: 1260	aaacattcctttaacaatt	9488	9507	1	5
SEQ ID NO: 258	aaaatagctatttgctaata	6693	6712	SEQ ID NO: 1261	tattgaaaatattgatttt	6806	6825	1	5
SEQ ID NO: 259	aaaattaaaaagtccttgat	6731	6750	SEQ ID NO: 1262	atcatatccgtgtaatttt	6757	6776	1	5
SEQ ID NO: 260	ttgaaaatattgattttaa	6808	6827	SEQ ID NO: 1263	ttaatcttcataagttcaa	13171	13190	1	5
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SEQ ID NO: 268	atttattgatgatgctgic	7295	7314	SEQ ID NO: 1271	gacatgttgataaagaaat	7371	7390	1	5
SEQ ID NO: 269	gaattatcttttaaaacat	7326	7345	SEQ ID NO: 1272	atgtatcaaatggacattc	7677	7696	1	5
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SEQ ID NO: 271	ttgcagtgtatctggaaag	7540	7559	SEQ ID NO: 1274	ctttcacatttagatgcaa	8412	8431	1	5
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SEQ ID NO: 273	acacctgattttatagtcc	7950	7969	SEQ ID NO: 1276	ggactcaaggataacgtgt	12606	12625	1	5
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SEQ ID NO: 298	agaagcaaatctggatttc	9467	9486	SEQ ID NO: 1301	gaaatcttcaatttattct	13813	13832	1	5
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SEQ ID NO: 310	cacttactgaattccaag	10664	10683	SEQ ID NO: 1313	cttgaacacaaagtcagtg	6000	6019	1	5
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SEQ ID NO: 313	agctggatgtaaccaccag	11176	11195	SEQ ID NO: 1316	ctggattccacatgcagct	11847	11866	1	5
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SEQ ID NO: 334	attcaagcacciccgggaag	245	264	SEQ ID NO: 1337	cttcataagttcaatgaat	13176	13195	2	4
SEQ ID NO: 335	gactgctgattcaagaagt	308	327	SEQ ID NO: 1338	acttcccaactctcaagtc	13407	13426	2	4
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SEQ ID NO: 337	agaaagatgaacctactta	547	566	SEQ ID NO: 1340	taaglatgatttcaattct	10490	10509	2	4



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SEQ ID NO: 354	tgaatacagccaggacttg	6080	6099	SEQ ID NO: 1357	caagagcacacgggtcttca	10679	10698	2	4
SEQ ID NO: 355	catcaataattgatcaattt	6413	6432	SEQ ID NO: 1358	aaattccctgaagttgatg	11478	11497	2	4
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SEQ ID NO: 358	ttcaggctcttcagaaagc	7921	7940	SEQ ID NO: 1361	gcttgctaacctctctgaa	12304	12323	2	4
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SEQ ID NO: 365	ctgagtgcccttctcgggtt	14	33	SEQ ID NO: 1368	aaccgtgcctgaatctcag	11549	11568	1	4
SEQ ID NO: 366	tctcgggtgctgccgctga	25	44	SEQ ID NO: 1369	tcagctgacctcatcgaga	2160	2179	1	4
SEQ ID NO: 367	caggccgcagcccaggagc	82	101	SEQ ID NO: 1370	gctctgcagcttcatcctg	368	387	1	4
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SEQ ID NO: 370	ctggctgttccaaaagatg	219	238	SEQ ID NO: 1373	catcctgaagaccagccag	380	399	1	4
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SEQ ID NO: 372	tccagtgagtgccctggga	291	310	SEQ ID NO: 1375	tcccgagccaaggctgga	2675	2694	1	4
SEQ ID NO: 373	agggtgagctggagggtcc	346	365	SEQ ID NO: 1376	ggaacctctccctcacct	4728	4747	1	4
SEQ ID NO: 374	tgagctggagggttccccag	350	369	SEQ ID NO: 1377	ctgggaggcatgatgctca	9163	9182	1	4
SEQ ID NO: 375	tctgcagcttcatcctgaa	370	389	SEQ ID NO: 1378	ticaaatataatcggcaga	3261	3280	1	4

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SEQ ID NO: 380	catcaagagggggcatcatt	575	594	SEQ ID NO: 1383	aatgggtcaagttcctgatg	2277	2296	1	4
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SEQ ID NO: 386	aggaagggcaatgtggcaa	693	712	SEQ ID NO: 1389	ttgcaagcaagtctttcct	3005	3024	1	4
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SEQ ID NO: 388	caatgtggcaacagaaata	701	720	SEQ ID NO: 1391	tattcttctttccaattg	13826	13845	1	4
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SEQ ID NO: 390	agagacctgggccagtgtg	729	748	SEQ ID NO: 1393	cacattacatttggtctct	2930	2949	1	4
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SEQ ID NO: 392	gtgatcgcttcaagcccat	745	764	SEQ ID NO: 1395	atgggaaagccgccctcac	5209	5228	1	4
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SEQ ID NO: 395	ccttgtcaactctgatcag	811	830	SEQ ID NO: 1398	ctgagtgggtttatcaagg	12445	12464	1	4
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SEQ ID NO: 405	tgtttgaagactctccag	1082	1101	SEQ ID NO: 1408	ctggtaactactttaaaca	5487	5506	1	4
SEQ ID NO: 406	ttgaagactctccaggaac	1086	1105	SEQ ID NO: 1409	gttcaatgaatttatcaa	13184	13203	1	4
SEQ ID NO: 407	aactgaaaaaactaaccat	1102	1121	SEQ ID NO: 1410	atggcattttttgcaagtt	14006	14025	1	4
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SEQ ID NO: 410	tgagcaaaatatccagaga	1124	1143	SEQ ID NO: 1413	tctccagataaaaaactca	12201	12220	1	4
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SEQ ID NO: 412	tactgagctgagaggcctc	1166	1185	SEQ ID NO: 1415	gagggtagtcatcacagta	10329	10348	1	4
SEQ ID NO: 413	gcctcagtgatgaagcagt	1180	1199	SEQ ID NO: 1416	actgttgactcaggaaggc	12572	12591	1	4



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SEQ ID NO: 416	tctctcttgccacagctga	1203	1222	SEQ ID NO: 1419	tcagctgacctcatcgaga	2160	2179	1	4
SEQ ID NO: 417	tgccacagctgattgaggt	1210	1229	SEQ ID NO: 1420	acctgcaccaaagctggca	13955	13974	1	4
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SEQ ID NO: 427	atgaagattacacctattt	1552	1571	SEQ ID NO: 1430	aaatgaaagtaaagatcat	8110	8129	1	4
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SEQ ID NO: 439	aatatcttgaactcagaag	1905	1924	SEQ ID NO: 1442	cttccattctgaatatatt	13370	13389	1	4
SEQ ID NO: 440	ctcagaagaattggatata	1916	1935	SEQ ID NO: 1443	gataaaagattactttgag	7265	7284	1	4
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SEQ ID NO: 443	tggatatccaagatctgaa	1927	1946	SEQ ID NO: 1446	ttcacataccagaattcca	8317	8336	1	4
SEQ ID NO: 444	atatccaagatctgaaaaa	1930	1949	SEQ ID NO: 1447	ttttaaccagtcagatat	10177	10196	1	4
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SEQ ID NO: 737	ctgagagttccagtggagt	283	302	SEQ ID NO: 1740	actcaatggtgaaattcag	7457	7476	2	3
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SEQ ID NO: 827	aaactgctccactcacttt	662	681	SEQ ID NO: 1830	aaagaaacagcatttgttt	4532	4551	1	3
SEQ ID NO: 828	actcactttaccgtcaaga	672	691	SEQ ID NO: 1831	tcttacttttccattgagt	10572	10591	1	3
SEQ ID NO: 829	ctttaccgtcaagacgagg	677	696	SEQ ID NO: 1832	cctccagctcctgggaaag	2483	2502	1	3
SEQ ID NO: 830	ttaccgtcaagacgaggaa	679	698	SEQ ID NO: 1833	ttcctaaagctggatgtaa	11169	11188	1	3
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SEQ ID NO: 834	ggaagggcaatgtggcaac	694	713	SEQ ID NO: 1837	gttgctottaaggacttcc	13356	13375	1	3
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SEQ ID NO: 836	caggcatcagcccacttgc	769	788	SEQ ID NO: 1839	gcaagtctttcctggcctg	3011	3030	1	3
SEQ ID NO: 837	aggcatcagcccacttgc	770	789	SEQ ID NO: 1840	agcaagtctttcctggcct	3010	3029	1	3
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SEQ ID NO: 839	gtcaactctgacagcagc	815	834	SEQ ID NO: 1842	gctgactttaaactctgac	4811	4830	1	3
SEQ ID NO: 840	ggacgctaagaggaagcat	857	876	SEQ ID NO: 1843	atgcactgtttctgagtcc	9331	9350	1	3
SEQ ID NO: 841	aaggagcaacacctcttcc	894	913	SEQ ID NO: 1844	ggaatatcttagcatcctt	13457	13476	1	3
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SEQ ID NO: 844	aacacctcttctgccttt	901	920	SEQ ID NO: 1847	aaagcaggccgaagctggt	1067	1086	1	3
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SEQ ID NO: 902	agaacttgtggcttccca	1879	1898	SEQ ID NO: 1905	tgggcctgcccagattct	8901	8920	1	3
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SEQ ID NO: 913	gtcatggacttcagaaaat	1989	2008	SEQ ID NO: 1916	atttgaaagaataaatgac	7028	7047	1	3
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SEQ ID NO: 915	aactctacaaatctgttic	2023	2042	SEQ ID NO: 1918	gaaaaaggggattgaagtt	10276	10295	1	3
SEQ ID NO: 916	aaatagaagggaatcttat	2071	2090	SEQ ID NO: 1919	ataagcaaactgttaattt	5449	5468	1	3
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SEQ ID NO: 2298	gtgctacgtaattctcagg	12993	13012	SEQ ID NO: 2604	cctgcaccaaagctggcac	13956	13975	1	3
SEQ ID NO: 2299	agctgaaagagatgaaatt	13057	13076	SEQ ID NO: 2605	aatattatcaaaacagagct	13192	13211	1	3
SEQ ID NO: 2300	aatctactatcttattaa	13072	13091	SEQ ID NO: 2606	ttaaaagaaattctcaatt	13807	13826	1	3
SEQ ID NO: 2301	ttttaaattgttgaaagaa	13142	13161	SEQ ID NO: 2607	ttctctctatgggaaaaaa	9558	9577	1	3
SEQ ID NO: 2302	taattctcataagttcaat	13172	13191	SEQ ID NO: 2608	attgagattccctccatta	11694	11713	1	3
SEQ ID NO: 2303	atatatttgatccaagtata	13271	13290	SEQ ID NO: 2609	tataagcagaagcacatat	13929	13948	1	3
SEQ ID NO: 2304	tgaatattatgaacttga	13303	13322	SEQ ID NO: 2610	tcaaccttaattgatttca	8287	8306	1	3
SEQ ID NO: 2305	caattctgcacagaaata	13434	13453	SEQ ID NO: 2611	tattctcttttccaattg	13826	13845	1	3
SEQ ID NO: 2306	agaagattgcagagcttct	13501	13520	SEQ ID NO: 2612	gaaatctcaatttattct	13813	13832	1	3
SEQ ID NO: 2307	gaagaaaataattctgat	13562	13581	SEQ ID NO: 2613	atcagttcagataaaacttc	7991	8010	1	3
SEQ ID NO: 2308	ttgacctgtccattcaaaa	13672	13691	SEQ ID NO: 2614	tttgagaatgaattcaa	10414	10433	1	3
SEQ ID NO: 2309	tcaaaaactaccacacattt	13685	13704	SEQ ID NO: 2615	aaattccttgacatgttga	7362	7381	1	3
SEQ ID NO: 2310	tttttaaaagaaatcttc	13803	13822	SEQ ID NO: 2616	gaagtgtcagtggaacaaa	10374	10393	1	3
SEQ ID NO: 2311	aggatctgagttattttgc	14035	14054	SEQ ID NO: 2617	gcaagggtcactgttctct	7856	7875	1	3
SEQ ID NO: 2312	tttgctaaacttgggggag	14049	14068	SEQ ID NO: 2618	ctcccaggacotttcaaa	9834	9853	1	3

# = Match Number

B = Middle Matching Bases

Table 9. Selected palindromic sequences from human ApoB

	Source	Start Index	End Index	Match	Start Index	End Index	#	B
SEQ ID NO: 2619	ggccattccagaaggggaag	517	536	SEQ ID NO: 3948	cttccgttctgtaatggcc	5803	5822	1 9
SEQ ID NO: 2620	tgccatctcgagagttcca	4107	4126	SEQ ID NO: 3949	tggaactctctccatggca	10884	10903	1 8
SEQ ID NO: 2621	catgtcaaacactttgtta	7064	7083	SEQ ID NO: 3950	taacaaattccttgacatg	7366	7385	1 8
SEQ ID NO: 2622	ttgttataaatcttattg	7076	7095	SEQ ID NO: 3951	caataagatcaatagcaaa	8998	9017	1 8
SEQ ID NO: 2623	tctggaaaagggcatgga	8888	8907	SEQ ID NO: 3959	tccatgtcccatttacaga	11364	11383	1 8
SEQ ID NO: 2624	cagctctgttcagggtcca	10908	10927	SEQ ID NO: 3960	tggacotgcaccaaagctg	13960	13979	1 8
SEQ ID NO: 2625	ggaggtlccccagctctgc	364	383	SEQ ID NO: 3961	gcagccctgggaaaactcc	6455	6474	1 7
SEQ ID NO: 2626	ctgtttgaagacictcca	1089	1108	SEQ ID NO: 3962	tggagggtagtcataacag	10335	10354	1 7
SEQ ID NO: 2627	agtggctgaaacgtgtgca	1305	1324	SEQ ID NO: 3963	tcagagcttctgccact	13516	13535	1 7
SEQ ID NO: 2628	ccaaaatagaagggaatct	2076	2095	SEQ ID NO: 3964	agattccttgccctttgg	4008	4027	1 7
SEQ ID NO: 2629	tgaagagaagattgaattt	3628	3647	SEQ ID NO: 3965	aaattctctttcttttca	9220	9239	1 7
SEQ ID NO: 2630	agtgggtggcaacaccagca	4238	4257	SEQ ID NO: 3966	tgctagtggaggccaacact	10657	10676	1 7
SEQ ID NO: 2631	aaggctccacaagtcacat	5958	5977	SEQ ID NO: 3967	tgatgatctggaacctt	10732	10751	1 7
SEQ ID NO: 2632	gtcagccagggttatagca	7733	7752	SEQ ID NO: 3968	tgclaagaaccttactgac	7789	7808	1 7
SEQ ID NO: 2633	tgatatctggaaccttgaa	10735	10754	SEQ ID NO: 3969	ttcactgttctcgaaatca	7871	7890	1 7
SEQ ID NO: 2634	gtcaagttgagcaatttct	13431	13450	SEQ ID NO: 3970	agaaaaggcacaccttgac	11080	11099	1 7
SEQ ID NO: 2635	atccagatggaaaagggaa	13488	13507	SEQ ID NO: 3971	ttccaatttccctgtggat	3688	3707	1 7
SEQ ID NO: 2636	atttgttgtcaaagaagt	4551	4570	SEQ ID NO: 3972	acttcagagaaatacaaat	11409	11428	4 6
SEQ ID NO: 2637	ctggaaaatgtcagcctgg	212	231	SEQ ID NO: 3973	ccagacttccgtttaccag	8243	8262	2 6
SEQ ID NO: 2638	accaggaggttcttctca	1737	1756	SEQ ID NO: 3974	tgaagtgtagtctcctggt	5097	5116	2 6
SEQ ID NO: 2639	aaagaagttctgaaagaat	1964	1983	SEQ ID NO: 3975	attccatcacaaatccttt	9669	9688	2 6
SEQ ID NO: 2640	gctacagcttatggctcca	3578	3597	SEQ ID NO: 3976	tggatctaaatgcagtagc	11631	11650	2 6
SEQ ID NO: 2641	atcaatatgatcaatttg	6422	6441	SEQ ID NO: 3977	caaagaagtcaagattgat	4561	4580	2 6
SEQ ID NO: 2642	gaattatcttttaaacat	7334	7353	SEQ ID NO: 3978	atgtgttaacaaaatattc	11502	11521	2 6
SEQ ID NO: 2643	cgaggcccgctgctggc	138	157	SEQ ID NO: 3979	gccagaagtgagatcctcg	3515	3534	1 6
SEQ ID NO: 2644	acaactatgaggctgagag	279	298	SEQ ID NO: 3980	ctctgagcaacaaattgt	10317	10336	1 6
SEQ ID NO: 2645	gctgagagttccagtgag	290	309	SEQ ID NO: 3981	ctccatggcaaatgtcagc	10893	10912	1 6
SEQ ID NO: 2646	tgaagaaaaccaagaactc	456	475	SEQ ID NO: 3982	gagtcattgagggttctca	4937	4956	1 6
SEQ ID NO: 2647	cctacttacatcctgaaca	566	585	SEQ ID NO: 3983	tgttcataaggaggtagg	12774	12793	1 6
SEQ ID NO: 2648	ctacttacatcctgaacat	567	586	SEQ ID NO: 3984	atgttcataaggaggtag	12773	12792	1 6
SEQ ID NO: 2649	gagacagaagaagccaagc	623	642	SEQ ID NO: 3985	gcttggtttgccagtcic	2467	2486	1 6
SEQ ID NO: 2650	cactcactttacogtcaag	679	698	SEQ ID NO: 3986	cttgaacacaaagtcagtg	6008	6027	1 6
SEQ ID NO: 2651	ctgatcagcagcagccagt	830	849	SEQ ID NO: 3987	actgggaagtgttatcag	5245	5264	1 6
SEQ ID NO: 2652	actggacgctaagaggaag	862	881	SEQ ID NO: 3988	cttcccaagagaccagt	2898	2917	1 6
SEQ ID NO: 2653	agaggaagcatgtggcaga	873	892	SEQ ID NO: 3989	tctggcatttacttctct	5929	5948	1 6
SEQ ID NO: 2654	tgaagactctccaggaact	1095	1114	SEQ ID NO: 3990	agttgaaggagaciatcca	7224	7243	1 6
SEQ ID NO: 2655	ctctgagcaaaatatccag	1129	1148	SEQ ID NO: 3991	ctggttactgagctgagag	1169	1188	1 6
SEQ ID NO: 2656	atgaagcagtcacatctct	1197	1216	SEQ ID NO: 3992	agagctgccagtccttcat	10024	10043	1 6
SEQ ID NO: 2657	ttgccacagctgattgagg	1217	1236	SEQ ID NO: 3993	cctcctacagtgggtggcaa	4230	4249	1 6
SEQ ID NO: 2658	agctgattgagggtgccag	1224	1243	SEQ ID NO: 3994	ctggattccacatgcagct	11855	11874	1 6
SEQ ID NO: 2659	tgctccactcacatcctcc	1286	1305	SEQ ID NO: 3995	ggaggcttaagttcagca	7609	7628	1 6
SEQ ID NO: 2660	tgaacgtgtgcatgccaa	1311	1330	SEQ ID NO: 3996	tgggagagacaagtttca	6508	6527	1 6
SEQ ID NO: 2661	gacattgctaattacctga	1511	1530	SEQ ID NO: 3997	tcagaagctaagcaatgtc	7240	7259	1 6
SEQ ID NO: 2662	ttcttctcagactttcct	1746	1765	SEQ ID NO: 3998	aggagagtccaaatagaa	8506	8525	1 6
SEQ ID NO: 2663	ccaatatctgaactcaga	1911	1930	SEQ ID NO: 3999	tctgaattcattcaattgg	6493	6512	1 6
SEQ ID NO: 2664	aaagttagtgaagaagtt	1954	1973	SEQ ID NO: 4000	aaclaccctcactgccttt	2140	2159	1 6
SEQ ID NO: 2665	aagttagtgaagaagttc	1955	1974	SEQ ID NO: 4001	gaacctctggcatttactt	5924	5943	1 6
SEQ ID NO: 2666	aaagaagttctgaaagaat	1964	1983	SEQ ID NO: 4002	attctctggttaactactt	5490	5509	1 6



SEQ ID NO: 2667	ttggctataccaaagatg	2330	2349	SEQ ID NO: 4003	catcttaggcactgacaaa	5005	5024	1	6
SEQ ID NO: 2668	tgttgagaagctgattaaa	2389	2408	SEQ ID NO: 4004	tttagccatcggtcaaca	5708	5727	1	6
SEQ ID NO: 2669	caggaagggtcaaagaat	2569	2588	SEQ ID NO: 4005	attcccttaacaattcctg	9500	9519	1	6
SEQ ID NO: 2670	aggaagggtcaaagaatg	2570	2589	SEQ ID NO: 4006	cattcccttaacaattcct	9499	9518	1	6
SEQ ID NO: 2671	gaagggtcaaagaatgac	2572	2591	SEQ ID NO: 4007	gtcagctctcaggctcttc	7922	7941	1	6
SEQ ID NO: 2672	caaagaatgactttttct	2580	2599	SEQ ID NO: 4008	agaaggatggcatttttg	14008	14027	1	6
SEQ ID NO: 2673	catggagaatgccttigaa	2611	2630	SEQ ID NO: 4009	ttcagagccaaagtccatg	7127	7146	1	6
SEQ ID NO: 2674	ggagccaaggctggagtaa	2687	2706	SEQ ID NO: 4010	ttactccaacgccagctcc	3058	3077	1	6
SEQ ID NO: 2675	tcattccttcccaaagag	2892	2911	SEQ ID NO: 4011	ctctcggggcatctatga	5147	5166	1	6
SEQ ID NO: 2676	acclatgagctccagagag	3173	3192	SEQ ID NO: 4012	ctctcaagaccacagaggt	12984	13003	1	6
SEQ ID NO: 2677	gggcaaacgtcttacaga	3373	3392	SEQ ID NO: 4013	ctgaaagacaacgtgccc	12325	12344	1	6
SEQ ID NO: 2678	accctggacattcagaaca	3395	3414	SEQ ID NO: 4014	tggtgctaaggttcagggt	5683	5702	1	6
SEQ ID NO: 2679	atgggagacctaagttgtg	3437	3456	SEQ ID NO: 4015	cacaaattagtttcacat	8949	8968	1	6
SEQ ID NO: 2680	gatgaagagaagattgaat	3626	3645	SEQ ID NO: 4016	attccagcttccccacatc	8338	8357	1	6
SEQ ID NO: 2681	caatgtagataccaaaaaa	3664	3683	SEQ ID NO: 4017	tttttggaatgccattg	8651	8670	1	6
SEQ ID NO: 2682	glagataccaaaaaatga	3668	3687	SEQ ID NO: 4018	tcattgtgatgggtctctac	4379	4398	1	6
SEQ ID NO: 2683	gcttcagttcatttggact	4517	4536	SEQ ID NO: 4019	agtcaagaaggacttaagc	5312	5331	1	6
SEQ ID NO: 2684	ttgtttgtcaaagaagtc	4552	4571	SEQ ID NO: 4020	gacttcagagaaatacaaa	11408	11427	1	6
SEQ ID NO: 2685	ttgtttgtcaaagaagtc	4553	4572	SEQ ID NO: 4021	tgacttcagagaaatacaa	11407	11426	1	6
SEQ ID NO: 2686	tggaatgggaaactcgct	5854	5873	SEQ ID NO: 4022	agcgagaatcacctgccca	8227	8246	1	6
SEQ ID NO: 2687	aacctctggcatttacttt	5925	5944	SEQ ID NO: 4023	aaaggagatgtcaagggtt	10607	10626	1	6
SEQ ID NO: 2688	catttactttctctcatga	5934	5953	SEQ ID NO: 4024	tcatttgaagaataaatg	7034	7053	1	6
SEQ ID NO: 2689	aaagtcagtgccctgctta	6017	6036	SEQ ID NO: 4025	taagaaccttactgacttt	7792	7811	1	6
SEQ ID NO: 2690	tccatttttgagacctt	6330	6349	SEQ ID NO: 4026	aaggacttcaggaatggga	12012	12031	1	6
SEQ ID NO: 2691	catcaatattgatcaattt	6421	6440	SEQ ID NO: 4027	aaattaaaaagctttagt	6740	6759	1	6
SEQ ID NO: 2692	taaagatagttatgattta	6673	6692	SEQ ID NO: 4028	taaaccaaaacttggttta	9027	9046	1	6
SEQ ID NO: 2693	tattgatgaaatcattgaa	6721	6740	SEQ ID NO: 4029	ttcaaagacttaaaaaata	8015	8034	1	6
SEQ ID NO: 2694	atgatctacatttgttat	6798	6817	SEQ ID NO: 4030	ataaagaaattaaagtcac	7388	7407	1	6
SEQ ID NO: 2695	agagacacatacagaatat	6927	6946	SEQ ID NO: 4031	atatattgtcagtgccctc	13390	13409	1	6
SEQ ID NO: 2696	gacacatacagaatataga	6930	6949	SEQ ID NO: 4032	tctaaattcagttcttctc	11335	11354	1	6
SEQ ID NO: 2697	agcatgtcaaacactttgt	7062	7081	SEQ ID NO: 4033	acaaagtcagtgccctgct	6015	6034	1	6
SEQ ID NO: 2698	tttttagaggaaaccaagg	7523	7542	SEQ ID NO: 4034	cctttgtgtacacaaaaaa	11238	11257	1	6
SEQ ID NO: 2699	tttagaggaaaccaaggc	7524	7543	SEQ ID NO: 4035	gcctttgtgtacacaaaaa	11237	11256	1	6
SEQ ID NO: 2700	ggaagatagacttctgaa	9315	9334	SEQ ID NO: 4036	ttcagaaatactgttttcc	12832	12851	1	6
SEQ ID NO: 2701	cactgttctgagtcaccag	9342	9361	SEQ ID NO: 4037	ctgggacctaccaagagt	12531	12550	1	6
SEQ ID NO: 2702	cacaaatccttggctgtg	9676	9695	SEQ ID NO: 4038	cacatttcaaggaattgtg	10071	10090	1	6
SEQ ID NO: 2703	ttcctggatacactgttcc	9861	9880	SEQ ID NO: 4039	ggaactgttgactcaggaa	12577	12596	1	6
SEQ ID NO: 2704	gaaatcicaagctttctct	10050	10069	SEQ ID NO: 4040	agagccaggctcagacttc	11052	11071	1	6
SEQ ID NO: 2705	tttctcatcttcatctgt	10218	10237	SEQ ID NO: 4041	acagctgaaagagatgaaa	13063	13082	1	6
SEQ ID NO: 2706	ttaccgctaaaggagcag	10529	10548	SEQ ID NO: 4042	ctgcacgctttgaggtaga	11769	11788	1	6
SEQ ID NO: 2707	ctaccgctaaaggagcagt	10530	10549	SEQ ID NO: 4043	actgcacgctttgaggtag	11768	11787	1	6
SEQ ID NO: 2708	agggcctcttttcaccaa	10839	10858	SEQ ID NO: 4044	ttggccaggaagtggccct	10965	10984	1	6
SEQ ID NO: 2709	ttctccaicctgtataaag	11273	11292	SEQ ID NO: 4045	cttttcaccaacggagaa	10846	10865	1	6
SEQ ID NO: 2710	gaaaaacaaagcagattat	11824	11843	SEQ ID NO: 4046	ataaactgcaagatttttc	13608	13627	1	6
SEQ ID NO: 2711	actcactcattgattttct	12690	12709	SEQ ID NO: 4047	agaaaatcaggatctgagt	14035	14054	1	6
SEQ ID NO: 2712	taaaactaatagatgtaatc	12898	12917	SEQ ID NO: 4048	gattaccaccagcagttta	13586	13605	1	6
SEQ ID NO: 2713	caaaacgagcttcaggaag	13208	13227	SEQ ID NO: 4049	ctcgtgagaatattttg	13268	13287	1	6
SEQ ID NO: 2714	tggaataatgtcagtggtt	2374	2393	SEQ ID NO: 4050	aacacttacttgaaatcca	10670	10689	3	5
SEQ ID NO: 2715	gatttgaaatccaaagaag	2408	2427	SEQ ID NO: 4051	cttcagagaaatacaaatc	11410	11429	3	5
SEQ ID NO: 2716	atttgaaatccaaagaagt	2409	2428	SEQ ID NO: 4052	acttcagagaaatacaaat	11409	11428	3	5

SEQ ID NO: 2717	atcaacagccgcttcttg	998	1017	SEQ ID NO: 4053	caaagaagtcaagattgat	4561	4580	2	5
SEQ ID NO: 2718	tgtttgaagactctccag	1090	1109	SEQ ID NO: 4054	ctggaaagttaaacaaca	6963	6982	2	5
SEQ ID NO: 2719	cccttctgatagatgtgt	1332	1351	SEQ ID NO: 4055	accaaagctggcaccaggg	13969	13988	2	5
SEQ ID NO: 2720	tgagcaagtgaagaacttt	1876	1895	SEQ ID NO: 4056	aaagccattcagctctca	12971	12990	2	5
SEQ ID NO: 2721	atttgaatccaaagaagt	2409	2428	SEQ ID NO: 4057	acttttctaaacttgaaat	9063	9082	2	5
SEQ ID NO: 2722	atccaaagaagtcocggaa	2416	2435	SEQ ID NO: 4058	ttccgggggaaacctgggat	12729	12748	2	5
SEQ ID NO: 2723	agagcctaccctccgcatct	2438	2457	SEQ ID NO: 4059	agatggtaacgttagcctct	11929	11948	2	5
SEQ ID NO: 2724	aatgccttgaactcccca	2618	2637	SEQ ID NO: 4060	tggaactacaatttcatt	7020	7039	2	5
SEQ ID NO: 2725	gaagtccaaattccggatt	3305	3324	SEQ ID NO: 4061	aattctcaatttatcttc	13823	13842	2	5
SEQ ID NO: 2726	tgcaagcagaagccagaag	3504	3523	SEQ ID NO: 4062	cttcaggttccatcgtgca	11384	11403	2	5
SEQ ID NO: 2727	gaagagaagattgaatttg	3629	3648	SEQ ID NO: 4063	caaaacctactgtctcttc	10467	10486	2	5
SEQ ID NO: 2728	atgctaaaggcacatatgg	4605	4624	SEQ ID NO: 4064	ccatataaagtcagcat	12664	12683	2	5
SEQ ID NO: 2729	tcctcacctccacctctg	4745	4764	SEQ ID NO: 4065	cagattctcagatgaggga	8920	8939	2	5
SEQ ID NO: 2730	atttacagctctgacaagt	5435	5454	SEQ ID NO: 4066	acttttctaaacttgaaat	9063	9082	2	5
SEQ ID NO: 2731	aggagcctacaaaataat	5602	5621	SEQ ID NO: 4067	attatgttgaaacagtcct	11838	11857	2	5
SEQ ID NO: 2732	aaagctgaagcacatcaat	6409	6428	SEQ ID NO: 4068	attgttgctcatctccttt	10202	10221	2	5
SEQ ID NO: 2733	ctgctggaaacaacgagaa	9426	9445	SEQ ID NO: 4069	ttctgattaccaccagcag	13582	13601	2	5
SEQ ID NO: 2734	ttgaaggaattctgaaaa	9590	9609	SEQ ID NO: 4070	ttttaaagaaatctcaa	13813	13832	2	5
SEQ ID NO: 2735	gaagtaaaagaaaatttg	10751	10770	SEQ ID NO: 4071	caaaacctactgtctcttc	10467	10486	2	5
SEQ ID NO: 2736	tgaagaagatggcaaat	11992	12011	SEQ ID NO: 4072	aaatgtcagctctgttca	10902	10921	2	5
SEQ ID NO: 2737	aggatctgagttatttgc	14043	14062	SEQ ID NO: 4073	gcaagtcagcccagttcct	10928	10947	2	5
SEQ ID NO: 2738	gtgcccttctcggttgctg	26	45	SEQ ID NO: 4074	cagccattgacatgagcac	5748	5767	1	5
SEQ ID NO: 2739	ggcgctgcctgcgctgctg	154	173	SEQ ID NO: 4075	cagctccacagactccgcc	3070	3089	1	5
SEQ ID NO: 2740	ctgcgctgctgctgctgct	162	181	SEQ ID NO: 4076	agcagaaggtgcgaagcag	3232	3251	1	5
SEQ ID NO: 2741	gctgctggcgggcgccagg	178	197	SEQ ID NO: 4077	cctggattccacatgcagc	11854	11873	1	5
SEQ ID NO: 2742	aagaggaaatgtcgaaaa	201	220	SEQ ID NO: 4078	ttttcttactacatctt	2592	2611	1	5
SEQ ID NO: 2743	ctggaaaatgtcagcctgg	212	231	SEQ ID NO: 4079	ccagactccacatcccag	3923	3942	1	5
SEQ ID NO: 2744	tggagtccctgggactgct	304	323	SEQ ID NO: 4080	agcatgcctagtttctcca	9953	9972	1	5
SEQ ID NO: 2745	ggagtccctgggactgctg	305	324	SEQ ID NO: 4081	cagcatgcctagtttctcc	9952	9971	1	5
SEQ ID NO: 2746	tgggactgctgattcaaga	313	332	SEQ ID NO: 4082	cttccatcacttgaccca	2050	2069	1	5
SEQ ID NO: 2747	ctgctgattcaagaagtgc	318	337	SEQ ID NO: 4083	gcacaccttgacattgcag	11087	11106	1	5
SEQ ID NO: 2748	tgccaccaggatcaactgc	334	353	SEQ ID NO: 4084	gcaggctgaactggtggca	2725	2744	1	5
SEQ ID NO: 2749	gccaccaggatcaactgca	335	354	SEQ ID NO: 4085	tgaggctgaactggtggc	2724	2743	1	5
SEQ ID NO: 2750	tgcaagggtgagctggagg	350	369	SEQ ID NO: 4086	cctccacctctgatctgca	4752	4771	1	5
SEQ ID NO: 2751	caagggtgagctggaggtt	352	371	SEQ ID NO: 4089	aaacctacatgaagcttg	13763	13782	1	5
SEQ ID NO: 2752	ctctcagcttcatctga	377	396	SEQ ID NO: 4090	tcaggaagcttctcaagag	13219	13238	1	5
SEQ ID NO: 2753	cagcttcatctgaagacc	382	401	SEQ ID NO: 4091	ggtcttgagttaaagtctg	4985	5004	1	5
SEQ ID NO: 2754	gcttcatctgaagaccag	384	403	SEQ ID NO: 4092	ctggacgctaagaggaagc	863	882	1	5
SEQ ID NO: 2755	tcatctgaagaccagcca	387	406	SEQ ID NO: 4093	tggcatggcattatgatga	3612	3631	1	5
SEQ ID NO: 2756	gaaaaccaagaactctgag	460	479	SEQ ID NO: 4094	cicaaccttaagtatttc	8294	8313	1	5
SEQ ID NO: 2757	agaactctgaggagtttgc	468	487	SEQ ID NO: 4095	gcaagctatacagatttct	8385	8404	1	5
SEQ ID NO: 2758	tctgaggagtttgctgcag	473	492	SEQ ID NO: 4096	ctgcagggggtccccaga	2534	2553	1	5
SEQ ID NO: 2759	tttgctgcagccatgtcca	482	501	SEQ ID NO: 4097	tggaagtgtcagtgga	10380	10399	1	5
SEQ ID NO: 2760	caagaggggcatcatttct	586	605	SEQ ID NO: 4098	agaataaatgacgttcttg	7043	7062	1	5
SEQ ID NO: 2761	tcactttaccgtcaagacg	682	701	SEQ ID NO: 4099	cgctacactatcatgtga	4368	4387	1	5
SEQ ID NO: 2762	ttaccgtcaagacgagga	686	705	SEQ ID NO: 4100	tccttgacatgttgataaa	7374	7393	1	5
SEQ ID NO: 2763	cactggacgctaagaggaa	861	880	SEQ ID NO: 4101	ttccagaaagcagccagtg	12506	12525	1	5
SEQ ID NO: 2764	aggaagcatgtggcagaag	875	894	SEQ ID NO: 4102	cttcatacacattaatcct	9996	10015	1	5
SEQ ID NO: 2765	caaggagcaacacctcttc	901	920	SEQ ID NO: 4103	gaagtagtactgcatcttg	6843	6862	1	5



SEQ ID NO: 2766	acagacttgaaactgaa	967	986	SEQ ID NO: 4104	ttcaattcttcaatgctgt	10508	10527	1	5
SEQ ID NO: 2767	tgaagaagcagtcacatct	1195	1214	SEQ ID NO: 4105	agatttgaggattccatca	7984	8003	1	5
SEQ ID NO: 2768	agcagtcacatctctcttg	1201	1220	SEQ ID NO: 4106	caaggagaaactgactgct	6532	6551	1	5
SEQ ID NO: 2769	ccagcccatcactttaca	1239	1258	SEQ ID NO: 4107	tgtagtctcctgggtgctgg	5102	5121	1	5
SEQ ID NO: 2770	ctccactcacatccctccag	1288	1307	SEQ ID NO: 4108	ctggagcttagtaatggag	8717	8736	1	5
SEQ ID NO: 2771	catgccaaccccccttctga	1322	1341	SEQ ID NO: 4109	tcagatgaggggaacacatg	8927	8946	1	5
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SEQ ID NO: 2773	tcaacatggcgagggatca	1407	1426	SEQ ID NO: 4111	tgatcccacctctcatga	2973	2992	1	5
SEQ ID NO: 2774	ccaccttgatgcgctgag	1437	1456	SEQ ID NO: 4112	ctcaggggatcgaagggtgg	8195	8214	1	5
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SEQ ID NO: 2781	tgagcaagtgaagaacttt	1876	1895	SEQ ID NO: 4119	aaagtgccacttttactca	6191	6210	1	5
SEQ ID NO: 2782	agcaagtgaagaactttgt	1878	1897	SEQ ID NO: 4120	acaaagtgcagtgccctgct	6015	6034	1	5
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SEQ ID NO: 2793	ctttggctataccaaagat	2329	2348	SEQ ID NO: 4131	atctcgtgtctaggaaaag	5976	5995	1	5
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SEQ ID NO: 2800	agaatgactttttcttca	2583	2602	SEQ ID NO: 4138	tgaagtccggattcattct	11023	11042	1	5
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SEQ ID NO: 2823	aaaagcgatggccgggtca	3956	3975	SEQ ID NO: 4161	tgactcactcattgatttt	12688	12707	1	5
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SEQ ID NO: 2862	cttttactcagtgagccca	6200	6219	SEQ ID NO: 4200	tgggctaaacgtatgaaag	7835	7854	1	5
SEQ ID NO: 2863	tcattgatgcttttagagat	6225	6244	SEQ ID NO: 4201	atcttcataagttcaatga	13182	13201	1	5
SEQ ID NO: 2864	aaaaccaagatgttctc	6303	6322	SEQ ID NO: 4202	gagtgaaatgctgttttt	8638	8657	1	5

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SEQ ID NO: 2868	gaaaacgtacagagaaagc	6395	6414	SEQ ID NO: 4206	gctttctctccacatttc	10060	10079	1	5
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SEQ ID NO: 2876	aaaatagctattgctaata	6701	6720	SEQ ID NO: 4214	tattgaaaaattgatitt	6814	6833	1	5
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SEQ ID NO: 2934	agatggcattgtctcttg	11614	11633	SEQ ID NO: 4272	caaagctgagaagaaatct	12423	12442	1	5
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SEQ ID NO: 2987	tgctgctggcgggcgccag	177	196	SEQ ID NO: 4325	ctggatgtaaccaccagca	11186	11205	1	4
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SEQ ID NO: 2993	tctgcagcttcatcctgaa	378	397	SEQ ID NO: 4331	ttcaaatataatcggcaga	3269	3288	1	4
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SEQ ID NO: 3006	caatgtggcaacagaaata	709	728	SEQ ID NO: 4344	tattctcttttccaattg	13834	13853	1	4
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SEQ ID NO: 3061	tgatatccaagatctgaa	1935	1954	SEQ ID NO: 4401	ttcacataccagaattcca	8325	8344	1	4
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SEQ ID NO: 3065	aagatctgaaaaagttagt	1944	1963	SEQ ID NO: 4405	actaaattcccatggctt	4972	4991	1	4
SEQ ID NO: 3066	tgaaaaagttagtgaaga	1950	1969	SEQ ID NO: 4406	tcttctcgggaatttca	10630	10649	1	4
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SEQ ID NO: 3068	tcagaaaattctctcggaa	2007	2026	SEQ ID NO: 4408	ttcctttaacaattcctga	9501	9520	1	4
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SEQ ID NO: 3392	cttttgtaaagtatgataa	6285	6304	SEQ ID NO: 4733	ttattgctgaatccaaaag	13656	13675	2	3
SEQ ID NO: 3393	ttgtaaagiatgataaaaa	6288	6307	SEQ ID NO: 4734	tttcaagcaaatgcacaa	8539	8558	2	3
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SEQ ID NO: 3395	gattatctgaattcattca	6488	6507	SEQ ID NO: 4736	tgaagtagaccaacaaatc	7162	7181	2	3
SEQ ID NO: 3396	aattgggagagacaagttt	6506	6525	SEQ ID NO: 4737	aaactaaatgatctaaatt	11324	11343	2	3
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SEQ ID NO: 3406	gaggagcccgcagccag	50	69	SEQ ID NO: 4747	ctggatcacagagtccttc	3752	3771	1	3
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SEQ ID NO: 3408	ccaggccgcagccaggag	89	108	SEQ ID NO: 4749	ctcccgagccaaggctgg	2682	2701	1	3
SEQ ID NO: 3409	ggagccgccccaccgcagc	104	123	SEQ ID NO: 4750	gctgttttgaagactctcc	1088	1107	1	3
SEQ ID NO: 3410	gaagaggaaatgctggaaa	200	219	SEQ ID NO: 4751	tttcaagttcctgaccttc	8309	8328	1	3
SEQ ID NO: 3411	caaaagatgcgacccgatt	237	256	SEQ ID NO: 4752	aatcttattggggattttg	7085	7104	1	3
SEQ ID NO: 3412	attcaagcacctccggaag	253	272	SEQ ID NO: 4753	cttccacatttcaaggaat	10067	10086	1	3



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SEQ ID NO: 3417	actgcaaggttgagctgga	348	367	SEQ ID NO: 4758	tccactcacatccctcagct	1289	1308	1	3
SEQ ID NO: 3418	ccagctctgcagcttcatc	373	392	SEQ ID NO: 4759	gatgtggtcacctacctgg	1343	1362	1	3
SEQ ID NO: 3419	agcttcatctgaagacca	383	402	SEQ ID NO: 4760	tgggtgctggagaatgagct	5112	5131	1	3
SEQ ID NO: 3420	cttcatctgaagaccagc	385	404	SEQ ID NO: 4761	gctggagtaaaactggaag	2696	2715	1	3
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SEQ ID NO: 3438	aacatcaagagggggcatca	581	600	SEQ ID NO: 4779	tgataaaaaccaagatgtt	6298	6317	1	3
SEQ ID NO: 3439	acatcaagagggggcatcat	582	601	SEQ ID NO: 4780	atgataaaaaccaagatgt	6297	6316	1	3
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SEQ ID NO: 3442	gaagaagccaagcaagtgt	629	648	SEQ ID NO: 4783	acacctccacattccttc	8079	8098	1	3
SEQ ID NO: 3443	ttgtttctggataccgtgt	647	666	SEQ ID NO: 4784	acactaaatacttccacaa	8775	8794	1	3
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SEQ ID NO: 3445	aaactgctccactcacttt	670	689	SEQ ID NO: 4786	aaagaaacagcatttgttt	4540	4559	1	3
SEQ ID NO: 3446	actcactttaccgtcaaga	680	699	SEQ ID NO: 4787	tcttacttttccattgagt	10580	10599	1	3
SEQ ID NO: 3447	ctttaccgtcaagacgagg	685	704	SEQ ID NO: 4788	cctccagctcctgggaaag	2491	2510	1	3
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SEQ ID NO: 3450	cgaggaagggcaatgtggc	699	718	SEQ ID NO: 4791	gccagaagttagatcctcg	3515	3534	1	3
SEQ ID NO: 3451	gaggaagggcaatgtggca	700	719	SEQ ID NO: 4792	tgccagctcctcatgacctc	2476	2495	1	3
SEQ ID NO: 3452	ggaagggcaatgtggcaac	702	721	SEQ ID NO: 4793	gttgctcttaaggacttcc	13364	13383	1	3
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SEQ ID NO: 3455	aggcatcagcccacttgc	778	797	SEQ ID NO: 4796	agcaagtcttctggcct	3018	3037	1	3
SEQ ID NO: 3456	tcagcccacttgcctcat	783	802	SEQ ID NO: 4797	atgaaagtcaagcatctga	12668	12687	1	3
SEQ ID NO: 3457	gtcaactctgatcagcagc	823	842	SEQ ID NO: 4798	gctgactttaaaatctgac	4819	4838	1	3
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SEQ ID NO: 3461	caacacctcttctgcctt	908	927	SEQ ID NO: 4802	aaggctgactctgtgttg	4292	4311	1	3
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SEQ ID NO: 3465	tagcacaagtgcacagac	954	973	SEQ ID NO: 4806	gtctcttcgttctatgcta	4592	4611	1	3
SEQ ID NO: 3466	agcacaagtgcacagact	955	974	SEQ ID NO: 4807	agtctcttcgttctatgct	4591	4610	1	3
SEQ ID NO: 3467	gcacaagtgcacagactt	956	975	SEQ ID NO: 4808	aagtgtagtccttggtgc	5099	5118	1	3
SEQ ID NO: 3468	aacttgaagacacacacaaa	978	997	SEQ ID NO: 4809	tttgaggatccatcagtt	7987	8006	1	3
SEQ ID NO: 3469	gcttcttgggaaggtac	1008	1027	SEQ ID NO: 4810	gtacctactttggcaagc	8372	8391	1	3
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SEQ ID NO: 3474	agcgttttgaagactctc	1087	1106	SEQ ID NO: 4815	gagaacatactgggcagct	5880	5899	1	3
SEQ ID NO: 3475	tgaaaaaactaaccatctc	1113	1132	SEQ ID NO: 4816	gagaaaaatcaatgccttca	7112	7131	1	3
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SEQ ID NO: 3481	aagcagtcacatctctctt	1200	1219	SEQ ID NO: 4822	aagaggcagcttctggctt	12297	12316	1	3
SEQ ID NO: 3482	ctctcttgccacagctgat	1212	1231	SEQ ID NO: 4823	atcaaaagaagcccaagag	12946	12965	1	3
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SEQ ID NO: 3517	acaaaattgtccaaattct	1842	1861	SEQ ID NO: 4858	agaaacagcatttgittgt	4542	4561	1	3
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SEQ ID NO: 3521	tttgtggcttcccatattg	1892	1911	SEQ ID NO: 4862	caataagatcaatagcaaa	8998	9017	1	3
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SEQ ID NO: 3523	ttcccatattgccaatatc	1900	1919	SEQ ID NO: 4864	gatatacactaggaggaa	12745	12764	1	3
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SEQ ID NO: 3527	lccaagatctgaaaaagtt	1941	1960	SEQ ID NO: 4868	aacttccaactgtcatgga	1986	2005	1	3
SEQ ID NO: 3528	ctgaaaaagttagtgaag	1949	1968	SEQ ID NO: 4869	ctttgaagtcagcttcag	7915	7934	1	3
SEQ ID NO: 3529	agttagtgaagaagttct	1956	1975	SEQ ID NO: 4870	agaatctcaactccaact	1978	1997	1	3
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SEQ ID NO: 3710	atatgctgaaatgaaattt	5353	5372	SEQ ID NO: 5051	aaatagctattgctaata	6702	6721	1	3
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SEQ ID NO: 3717	gttaatttacagctacagc	5468	5487	SEQ ID NO: 5058	gctgcatgtggctggtaac	5578	5597	1	3
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SEQ ID NO: 3745	tttagagatgagagatgcc	6235	6254	SEQ ID NO: 5086	ggcatgatgtcatttaaa	9177	9196	1	3
SEQ ID NO: 3746	gagaagccccaagaattta	6257	6276	SEQ ID NO: 5087	taaagccattcagtcctc	12970	12989	1	3
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SEQ ID NO: 3857	ataagtacaaccaaattt	9405	9424	SEQ ID NO: 5198	aaatcaggatctgagttat	14038	14057	1	3
SEQ ID NO: 3858	acaacgagaacatlatgga	9435	9454	SEQ ID NO: 5199	tccattctgaatatattgt	13380	13399	1	3
SEQ ID NO: 3859	aggaataaatggagaagca	9463	9482	SEQ ID NO: 5200	tgctggaattgtcattcct	11734	11753	1	3
SEQ ID NO: 3860	agcaaatctggatttctta	9478	9497	SEQ ID NO: 5201	taagttctctgtacctgct	11719	11738	1	3
SEQ ID NO: 3861	tcctttaacaattcctgaa	9502	9521	SEQ ID NO: 5202	ttcaaaacgagcttcagga	13206	13225	1	3
SEQ ID NO: 3862	tttaacaattcctgaaatg	9505	9524	SEQ ID NO: 5203	catttgatttaagtgtaaa	9621	9640	1	3



SEQ ID NO: 3863	acacaataatcacaactcc	9534 9553	SEQ ID NO: 5204	ggagacagcatcttcgtgt	11211	11230	1	3
SEQ ID NO: 3864	aagatttctctctatggga	9561 9580	SEQ ID NO: 5205	icccagaaaaacctcttctt	3936	3955	1	3
SEQ ID NO: 3865	gaaaaaacaggcttgaagg	9578 9597	SEQ ID NO: 5206	ccttttacaattcattttc	13021	13040	1	3
SEQ ID NO: 3866	ttgaaggaattcttgaaaa	9590 9609	SEQ ID NO: 5207	ttttgagaatgaatttcaa	10422	10441	1	3
SEQ ID NO: 3867	tgaaggaattcttgaaaac	9591 9610	SEQ ID NO: 5208	gtttggctgataaattca	11291	11310	1	3
SEQ ID NO: 3868	agctcagtataagaaaaac	9640 9659	SEQ ID NO: 5209	gtttgataaglacaaagct	9805	9824	1	3
SEQ ID NO: 3869	tcaaatccttgacaggca	9720 9739	SEQ ID NO: 5210	tgccctgagcagaccattga	11688	11707	1	3
SEQ ID NO: 3870	atgaacaaaaaattagtt	9789 9808	SEQ ID NO: 5211	aactttgcaciatgtttcat	12762	12781	1	3
SEQ ID NO: 3871	aattcctggatacactgtt	9859 9878	SEQ ID NO: 5212	aacacatgaatcacaatt	8938	8957	1	3
SEQ ID NO: 3872	ttccagttgtcaatgttga	9876 9895	SEQ ID NO: 5213	tcaaaaacgagcttcaggaa	13207	13226	1	3
SEQ ID NO: 3873	aagtgtctccattcccat	9894 9913	SEQ ID NO: 5214	atgggaagtataagaactt	4842	4861	1	3
SEQ ID NO: 3874	gtcagcatgcctagtttct	9950 9969	SEQ ID NO: 5215	agaaaaggcacaccttgac	11080	11099	1	3
SEQ ID NO: 3875	ctgccatgggcaatattac	10113 10132	SEQ ID NO: 5216	gtaagaaaaatacagagcag	6440	6459	1	3
SEQ ID NO: 3876	tgaataccaatgctgaact	10167 10186	SEQ ID NO: 5217	agttgaaggagactattca	7224	7243	1	3
SEQ ID NO: 3877	tattgttgctcatctcctt	10201 10220	SEQ ID NO: 5218	aaggaaacataaactaata	12889	12908	1	3
SEQ ID NO: 3878	tggtgtcatctcctttct	10204 10223	SEQ ID NO: 5219	agaagaaatctgcagaaca	12431	12450	1	3
SEQ ID NO: 3879	tctgtcattgatgcactgc	10232 10251	SEQ ID NO: 5220	gcagtagactataagcaga	13928	13947	1	3
SEQ ID NO: 3880	ccacagctctgtctctgag	10305 10324	SEQ ID NO: 5221	ctcagggatctgaagggtg	8195	8214	1	3
SEQ ID NO: 3881	atttgggagggtagtcatt	10330 10349	SEQ ID NO: 5222	atgaagtagaccaacaaat	7161	7180	1	3
SEQ ID NO: 3882	atatggaagtgtcagtggc	10377 10396	SEQ ID NO: 5223	gccacactccaacgcataat	10778	10797	1	3
SEQ ID NO: 3883	tggaaataccaagtcaaaa	10453 10472	SEQ ID NO: 5224	ttttacaattcattttcca	13023	13042	1	3
SEQ ID NO: 3884	aagtcaaacctactgtct	10463 10482	SEQ ID NO: 5225	agacctagtgtattacactt	12859	12878	1	3
SEQ ID NO: 3885	actgtctcttctccatgg	10475 10494	SEQ ID NO: 5226	ccatgcaagtcagcccagt	10924	10943	1	3
SEQ ID NO: 3886	cttcctccatggaatttaa	10482 10501	SEQ ID NO: 5227	ttaatcgagagggtatgaag	7148	7167	1	3
SEQ ID NO: 3887	attcttcaatgctgtactc	10512 10531	SEQ ID NO: 5228	gagttgaggggtccgggaat	12242	12261	1	3
SEQ ID NO: 3888	ttgaccacaagcttagctt	10548 10567	SEQ ID NO: 5231	aagcgacacctcaatatcaa	12036	12055	1	3
SEQ ID NO: 3889	cctcacctcttacttttcc	10573 10592	SEQ ID NO: 5232	ggaactattgctagttagg	10649	10668	1	3
SEQ ID NO: 3890	agctgcagggcacttccaa	10710 10729	SEQ ID NO: 5233	ttgggaagaagaggcagct	12289	12308	1	3
SEQ ID NO: 3891	ttcaaaaattgatgatatc	10723 10742	SEQ ID NO: 5234	gatatacactagggaggaa	12745	12764	1	3
SEQ ID NO: 3892	gagaacatacaagcaaagc	10860 10879	SEQ ID NO: 5235	gcttggttttgcagctctc	2467	2486	1	3
SEQ ID NO: 3893	atggcaaatgtcagctctt	10897 10916	SEQ ID NO: 5236	aagagggtatttaaagccat	12960	12979	1	3
SEQ ID NO: 3894	tggcaaatgtcagctcttg	10898 10917	SEQ ID NO: 5237	caagagggtatttaaagcca	12959	12978	1	3
SEQ ID NO: 3895	ttgttcagggtccatgcaag	10914 10933	SEQ ID NO: 5238	cttggggggaggaggaaaca	14066	14085	1	3
SEQ ID NO: 3896	tggttcagggtccatgcaagt	10915 10934	SEQ ID NO: 5239	acttggggggaggaggaaaca	14065	14084	1	3
SEQ ID NO: 3897	agttccttccatgatttcc	10940 10959	SEQ ID NO: 5240	ggaatctgataggaaact	12256	12275	1	3
SEQ ID NO: 3898	tgctaactaagaaccag	10987 11006	SEQ ID NO: 5241	ctggatgtaaccaccagca	11186	11205	1	3
SEQ ID NO: 3899	actaagaaccagaagatca	10994 11013	SEQ ID NO: 5242	tgatcaagaacctgttagt	13347	13366	1	3
SEQ ID NO: 3900	ctaagaaccagaagatcag	10995 11014	SEQ ID NO: 5243	ctgatcaagaacctgttag	13346	13365	1	3
SEQ ID NO: 3901	cagaagatcagatggaaaa	11003 11022	SEQ ID NO: 5244	ttttcagaccaactctctg	13622	13641	1	3
SEQ ID NO: 3902	aaaaatgaagtccggattc	11018 11037	SEQ ID NO: 5245	gaatttgaaagttcgtttt	9280	9299	1	3
SEQ ID NO: 3903	gattcattctgggtctttc	11032 11051	SEQ ID NO: 5246	gaaaacctatgccttaac	13166	13185	1	3
SEQ ID NO: 3904	aagaaaaggcacaccttga	11079 11098	SEQ ID NO: 5247	tcaaaacctactgtctctt	10466	10485	1	3
SEQ ID NO: 3905	aaggacacctaaaggttcct	11115 11134	SEQ ID NO: 5248	aggacaccaaataaacctt	7572	7591	1	3
SEQ ID NO: 3906	ccagcattggtaggagaca	11199 11218	SEQ ID NO: 5249	tgtcaacaagtaccactgg	12370	12389	1	3
SEQ ID NO: 3907	ctttgtgtacacaaaaaac	11239 11258	SEQ ID NO: 5250	gtttttaaattgttgaaag	13148	13167	1	3
SEQ ID NO: 3908	ccatccctgtaaaagtttt	11277 11296	SEQ ID NO: 5251	aaaagggtcatggaaatgg	8893	8912	1	3
SEQ ID NO: 3909	tgatctaaattcagttctt	11332 11351	SEQ ID NO: 5252	aagatagtcagtcgatca	13334	13353	1	3
SEQ ID NO: 3910	aagaagctgagaacttcat	11432 11451	SEQ ID NO: 5253	atgagatcaacacaattctt	13110	13129	1	3
SEQ ID NO: 3911	tttgccctcaacctaccaa	11453 11472	SEQ ID NO: 5254	ttggtacgagttactcaaa	12641	12660	1	3
SEQ ID NO: 3912	cttgattcccttttttgag	11536 11555	SEQ ID NO: 5255	ctcaattttgattttcaag	8528	8547	1	3

SEQ ID NO: 3913	ttcacgcttccaaaaagtg	11591 11610	SEQ ID NO: 5256	cactcattgattttctgaa	12693	12712	1	3
SEQ ID NO: 3914	tgtttcagatggcattgct	11608 11627	SEQ ID NO: 5257	agcagattatgttgaaaca	11833	11852	1	3
SEQ ID NO: 3915	aatgcagtagccaacaaga	11639 11658	SEQ ID NO: 5258	tcttttcagcccagccatt	9231	9250	1	3
SEQ ID NO: 3916	ctgagcagaccattgagat	11691 11710	SEQ ID NO: 5259	atctgatgaggaaactcag	12259	12278	1	3
SEQ ID NO: 3917	tgagcagaccattgagatt	11692 11711	SEQ ID NO: 5260	aatctgatgaggaaactca	12258	12277	1	3
SEQ ID NO: 3918	ttgagattccctccattaa	11703 11722	SEQ ID NO: 5261	ttaatcttcataagttcaa	13179	13198	1	3
SEQ ID NO: 3919	acttggagtgccagtttga	11807 11826	SEQ ID NO: 5262	tcaattgggagagacaagt	6504	6523	1	3
SEQ ID NO: 3920	caaatttgaaggacttcag	12004 12023	SEQ ID NO: 5263	ctgagaacttcatcatttg	11438	11457	1	3
SEQ ID NO: 3921	agcccagcgttcaccgatc	12056 12075	SEQ ID NO: 5264	gatccaagtatagtggct	13286	13305	1	3
SEQ ID NO: 3922	cagcgttcaccgatcicca	12060 12079	SEQ ID NO: 5265	tggacctgcaccaaagctg	13960	13979	1	3
SEQ ID NO: 3923	ctccatctgcgctaccaga	12074 12093	SEQ ID NO: 5266	tctgatatacatcacggag	13711	13730	1	3
SEQ ID NO: 3924	atgaggaaactcagatcaa	12264 12283	SEQ ID NO: 5267	ttgagttgcccaccatcat	11667	11686	1	3
SEQ ID NO: 3925	aggcagcttctggcttgct	12300 12319	SEQ ID NO: 5268	agcaagtctttcctggcct	3018	3037	1	3
SEQ ID NO: 3926	tgaagacaacgtgcccaa	12327 12346	SEQ ID NO: 5269	ttgggagagacaagtttca	6508	6527	1	3
SEQ ID NO: 3927	tatgattatgtcaacaagt	12362 12381	SEQ ID NO: 5270	actttgcactatgttcata	12763	12782	1	3
SEQ ID NO: 3928	cattaggcaaattgatgat	12475 12494	SEQ ID NO: 5271	atcaacacaatcttcaatg	13115	13134	1	3
SEQ ID NO: 3929	ttgactcaggaaggccaag	12584 12603	SEQ ID NO: 5272	cttggtacgagttactcaa	12640	12659	1	3
SEQ ID NO: 3930	gaaacctgggatatacact	12736 12755	SEQ ID NO: 5273	agtgattacacttcttctc	12865	12884	1	3
SEQ ID NO: 3931	tccittcgagttaaggaaa	12877 12896	SEQ ID NO: 5274	tttctgccactgctcagga	13524	13543	1	3
SEQ ID NO: 3932	gccattcagttctcaaga	12974 12993	SEQ ID NO: 5275	tcttccgttctgtaatggc	5802	5821	1	3
SEQ ID NO: 3933	gtgtctacgtaattctcagg	13001 13020	SEQ ID NO: 5276	cctgcaccaaagctggcac	13964	13983	1	3
SEQ ID NO: 3934	agctgaaagagatgaaatt	13065 13084	SEQ ID NO: 5277	aatttattcaaaacgagct	13200	13219	1	3
SEQ ID NO: 3935	aatttacttatcttattaa	13080 13099	SEQ ID NO: 5278	ttaaaagaaatcttcaatt	13815	13834	1	3
SEQ ID NO: 3936	ttttaaattgttgaaagaa	13150 13169	SEQ ID NO: 5279	ttctctctatgggaaaaaa	9566	9585	1	3
SEQ ID NO: 3937	taatcttcataagttcaat	13180 13199	SEQ ID NO: 5280	attgagattccctccatta	11702	11721	1	3
SEQ ID NO: 3938	atattttgatccaagtata	13279 13298	SEQ ID NO: 5281	tataagcagaagcacatat	13937	13956	1	3
SEQ ID NO: 3939	tgaatatattatgaacttga	13311 13330	SEQ ID NO: 5282	tcaaccttaattgatttca	8295	8314	1	3
SEQ ID NO: 3940	caatttctgcacagaaata	13442 13461	SEQ ID NO: 5283	tatttcttctttccaattg	13834	13853	1	3
SEQ ID NO: 3941	agaagattgcagagcttctc	13509 13528	SEQ ID NO: 5284	gaaatcttcaatttattct	13821	13840	1	3
SEQ ID NO: 3942	gaagaaaataatttctgat	13570 13589	SEQ ID NO: 5285	atcagttcagataaaacttc	7999	8018	1	3
SEQ ID NO: 3943	ttgacctgtccattcaaaa	13680 13699	SEQ ID NO: 5286	ttttgagaatgaatttcaa	10422	10441	1	3
SEQ ID NO: 3944	tcaaaactaccacacattt	13693 13712	SEQ ID NO: 5287	aaattccttgacatgttga	7370	7389	1	3
SEQ ID NO: 3945	ttttttaaagaaatcttc	13811 13830	SEQ ID NO: 5288	gaagtgtcagtggaacaaa	10382	10401	1	3
SEQ ID NO: 3946	aggatctgagttatttgc	14043 14062	SEQ ID NO: 5289	gcaaggggtcactgttct	7864	7883	1	3
SEQ ID NO: 3947	tttgctaaacttgggggag	14057 14076	SEQ ID NO: 5290	ctccccaggacctttcaaa	9842	9861	1	3

Table 10. Selected palindromic sequences from human glucose-6-phosphatase

Source		Start Index	End Index	Match	Start Index	End Index	#	B
SEQ ID NO:	5291 tccatcttcaggaagctgt	222	241	SEQ ID NO:	5369 acagactcttcagatgga	1340	1359	1 6
SEQ ID NO:	5292 ccatcttcaggaagctgtg	223	242	SEQ ID NO:	5370 cacagactcttcagatgg	1339	1358	1 6
SEQ ID NO:	5293 cctctggccatgccatggg	417	436	SEQ ID NO:	5371 cccattttgaggccagagg	1492	1511	1 6
SEQ ID NO:	5294 ctctggccatgccatgggc	418	437	SEQ ID NO:	5372 gccattttgaggccagag	1491	1510	1 6
SEQ ID NO:	5295 ttgaatgtcatttgtggt	521	540	SEQ ID NO:	5373 accatacattatcattcaa	2945	2964	1 6
SEQ ID NO:	5296 tcagtaatgggggaccagc	1886	1905	SEQ ID NO:	5374 gctggctcgaactcctga	2731	2750	1 6
SEQ ID NO:	5297 tttactgtgcatacatgt	1956	1975	SEQ ID NO:	5375 acatctttgaaaagaaaaa	2983	3002	1 6
SEQ ID NO:	5298 tgaggtgccaaaggaaatga	50	69	SEQ ID NO:	5376 tcatgtctcagccctctca	2620	2639	1 5
SEQ ID NO:	5299 gaggtgccaaaggaaatgag	51	70	SEQ ID NO:	5377 ctcatgtctcagccctctc	2619	2638	1 5
SEQ ID NO:	5300 gggaaagataaagccgacc	487	506	SEQ ID NO:	5378 ggtcgccctggcttattccc	1295	1314	1 5
SEQ ID NO:	5301 tttctcatcaagtgtt	598	617	SEQ ID NO:	5379 aacatctttgaaaagaaaa	2982	3001	1 5
SEQ ID NO:	5302 cttcagccacatccacag	651	670	SEQ ID NO:	5380 ctgtggactctggagaaag	773	792	1 5
SEQ ID NO:	5303 tggactctggagaaagccc	776	795	SEQ ID NO:	5381 gggctggctctcaactcca	884	903	1 5
SEQ ID NO:	5304 agcctcctcaagaacctgg	848	867	SEQ ID NO:	5382 ccagattcttccactggct	2107	2126	1 5
SEQ ID NO:	5305 ggctggggctggctctca	878	897	SEQ ID NO:	5383 tgagccaccgcaccggggcc	2801	2820	1 5
SEQ ID NO:	5306 gagctactcccactggaa	1439	1458	SEQ ID NO:	5384 ttccaggtaggggccagctc	1676	1695	1 5
SEQ ID NO:	5307 agctaataagctattgag	1572	1591	SEQ ID NO:	5385 ctccagcctcctcagtagct	2626	2645	1 5
SEQ ID NO:	5308 gctaataagctattgaga	1573	1592	SEQ ID NO:	5386 tctcagcctcctcagtagc	2625	2644	1 5
SEQ ID NO:	5309 ctataatggctttaattata	1854	1873	SEQ ID NO:	5387 tatatttttagaatttttag	2683	2702	1 5
SEQ ID NO:	5310 ctgctttcttttttttc	2509	2528	SEQ ID NO:	5388 gaaaaatatatatgtgcag	2996	3015	1 5
SEQ ID NO:	5311 caatcaccaccaagcctgg	0	19	SEQ ID NO:	5389 ccagaatgggtccacattg	812	831	1 4
SEQ ID NO:	5312 agcctggaataactgcaag	12	31	SEQ ID NO:	5390 cttggatttctgaatggct	1987	2006	1 4
SEQ ID NO:	5313 gttccatcttcaggaagct	220	239	SEQ ID NO:	5391 agctcactcccactggaac	1440	1459	1 4
SEQ ID NO:	5314 tgggtgggttttgatactg	326	345	SEQ ID NO:	5392 cagtcctcccaccctacca	2425	2444	1 4
SEQ ID NO:	5315 acctgtgagactggaccag	392	411	SEQ ID NO:	5393 ctggagaaagcccagaggt	782	801	1 4
SEQ ID NO:	5316 gctgttacagaaactttca	638	657	SEQ ID NO:	5394 tgaatggtcttctgccagc	1474	1493	1 4
SEQ ID NO:	5317 acagcatctataatgccag	666	685	SEQ ID NO:	5395 ctgggtgttagacctctgt	758	777	1 4
SEQ ID NO:	5318 ggggtgttagacctctgtgg	760	779	SEQ ID NO:	5396 ccacattgacaccacaccc	823	842	1 4
SEQ ID NO:	5319 ggtgttagacctctgtgga	761	780	SEQ ID NO:	5397 tccacattgacaccacacc	822	841	1 4
SEQ ID NO:	5320 gtgttagacctctgtggac	762	781	SEQ ID NO:	5398 gtccacattgacaccacac	821	840	1 4
SEQ ID NO:	5321 gacctctgtggactctgg	767	786	SEQ ID NO:	5399 ccagatattgcactaggctc	2014	2033	1 4
SEQ ID NO:	5322 cctgggcacgctctttggc	862	881	SEQ ID NO:	5400 gccagctcacaagcccagg	1687	1706	1 4
SEQ ID NO:	5323 ctgggcacgctctttggcc	863	882	SEQ ID NO:	5401 ggccagctcacaagcccag	1686	1705	1 4
SEQ ID NO:	5324 ctggtcttctacgtctgt	1028	1047	SEQ ID NO:	5402 acaaaagcaagacttcag	1663	1682	1 4
SEQ ID NO:	5325 agagtgcggtagtgccct	1056	1075	SEQ ID NO:	5403 agggccaggattcctctct	2229	2248	1 4
SEQ ID NO:	5326 tgggcactggtatttgag	1217	1236	SEQ ID NO:	5404 ctcccactggaacagccca	1446	1465	1 4
SEQ ID NO:	5327 gaattaaatcacgcatggc	1267	1286	SEQ ID NO:	5405 gccaaccaagagcacattc	2311	2330	1 4
SEQ ID NO:	5328 tgttgctagaagtgggtt	1598	1617	SEQ ID NO:	5406 aaccatcctgctcataaca	2967	2986	1 4
SEQ ID NO:	5329 aggagctctgaatctgata	1764	1783	SEQ ID NO:	5407 tatcacattacatcatcct	2063	2082	1 4
SEQ ID NO:	5330 taaatggctttaattatat	1855	1874	SEQ ID NO:	5408 atatatgtgcagtatttta	3003	3022	1 4
SEQ ID NO:	5331 aaaatgacaaggggagggc	2215	2234	SEQ ID NO:	5409 gcccctcttgccctgtttt	2817	2836	1 4
SEQ ID NO:	5332 ttaaaggaaaagtcaacat	2330	2349	SEQ ID NO:	5410 atgtgcagtattttatlaa	3007	3026	1 4
SEQ ID NO:	5333 acatcttctctctttttt	2345	2364	SEQ ID NO:	5411 aaaagaaaaatatatatgt	2992	3011	1 4
SEQ ID NO:	5334 ttctacgtctcttcccca	197	216	SEQ ID NO:	5412 tgggccagccgcacaagaa	1116	1135	1 3
SEQ ID NO:	5335 tgggtagctgtgattggag	257	276	SEQ ID NO:	5413 ctcccactgggaacagccca	1446	1465	1 3



SEQ ID NO: 5336	gctgtgattggagactggc	263	282	SEQ ID NO: 5414	gccatgccatgggcacagc	423	442	1	3
SEQ ID NO: 5337	cacttccgtgccctgata	358	377	SEQ ID NO: 5415	tatcaccagggtggagtg	2548	2567	1	3
SEQ ID NO: 5338	acatctactctttccatct	464	483	SEQ ID NO: 5416	agatgggatttcatcatgt	2705	2724	1	3
SEQ ID NO: 5339	ctactctttccatcttca	468	487	SEQ ID NO: 5417	lgaatactctcacaagtag	1419	1438	1	3
SEQ ID NO: 5340	agataaagccgacctacag	492	511	SEQ ID NO: 5418	ctgttttcaatctcatct	2828	2847	1	3
SEQ ID NO: 5341	tgtgcagctgaatgtctgt	553	572	SEQ ID NO: 5419	acagaaactttcagccaca	644	663	1	3
SEQ ID NO: 5342	atgtctgtctgtcacgaat	564	583	SEQ ID NO: 5420	attcagggtatagctgacat	2038	2057	1	3
SEQ ID NO: 5343	ctgtcacgaatctaccttg	572	591	SEQ ID NO: 5421	caagggtgctaggattacag	2779	2798	1	3
SEQ ID NO: 5344	atcaagttgttgctggagt	606	625	SEQ ID NO: 5422	actcctgacctcaagtgat	2742	2761	1	3
SEQ ID NO: 5345	cagaaactttcagccacat	645	664	SEQ ID NO: 5423	atgtttcaattaggctctg	2185	2204	1	3
SEQ ID NO: 5346	actttcagccacatccaca	650	669	SEQ ID NO: 5424	tgtggcgtatcatgcaagt	1818	1837	1	3
SEQ ID NO: 5347	atgccagcctcaagaaata	678	697	SEQ ID NO: 5425	tatttttttactgtgcat	1950	1969	1	3
SEQ ID NO: 5348	agaaatattttctcattac	690	709	SEQ ID NO: 5426	gtaaataatgactcctttct	2283	2302	1	3
SEQ ID NO: 5349	gaaatattttctcattacc	691	710	SEQ ID NO: 5427	ggtaaataatgactccttct	2282	2301	1	3
SEQ ID NO: 5350	tgctgctcaagggactggg	744	763	SEQ ID NO: 5428	cccaagccaaccaagagca	2306	2325	1	3
SEQ ID NO: 5351	cctgtggactctggagaaa	772	791	SEQ ID NO: 5429	tttcatcatgttggccagg	2713	2732	1	3
SEQ ID NO: 5352	ggagaaagcccagagggtg	784	803	SEQ ID NO: 5430	ccaccgcaccgggcccctcc	2805	2824	1	3
SEQ ID NO: 5353	ttgaaacccccatccaag	1004	1023	SEQ ID NO: 5431	ctgaattcctgggctcaa	2405	2424	1	3
SEQ ID NO: 5354	cagatggagggtgccatact	1351	1370	SEQ ID NO: 5432	gatatgcagagtatttctg	2847	2866	1	3
SEQ ID NO: 5355	ggagctcactcccactgga	1438	1457	SEQ ID NO: 5433	tccacctgccttggcctcc	2760	2779	1	3
SEQ ID NO: 5356	ttgggtaatgttttgaaa	1553	1572	SEQ ID NO: 5434	tttctctatcccaagccaa	2297	2316	1	3
SEQ ID NO: 5357	gaagttgggtgttctgga	1606	1625	SEQ ID NO: 5435	tccaccccactggatcttc	2131	2150	1	3
SEQ ID NO: 5358	aaaagaaggctgcctaagg	1785	1804	SEQ ID NO: 5436	ccttgcctgcttttcttt	2503	2522	1	3
SEQ ID NO: 5359	aaagaaggctgcctaagga	1786	1805	SEQ ID NO: 5437	tccttgcctgcttttcttt	2502	2521	1	3
SEQ ID NO: 5360	aagaaggctgcctaaggag	1787	1806	SEQ ID NO: 5438	ctccttgcctgcttttctt	2501	2520	1	3
SEQ ID NO: 5361	agaaggctgcctaaggagg	1788	1807	SEQ ID NO: 5439	cctccttgcctgcttttct	2500	2519	1	3
SEQ ID NO: 5362	atttccttgatttctgaa	1982	2001	SEQ ID NO: 5440	ttcaattaggctctgaaat	2189	2208	1	3
SEQ ID NO: 5363	tccttataagcccagctct	2081	2100	SEQ ID NO: 5441	agagcacattcttaaagga	2319	2338	1	3
SEQ ID NO: 5364	ataagcccagctctgcttt	2086	2105	SEQ ID NO: 5442	aaagctgaagcctatttat	2889	2908	1	3
SEQ ID NO: 5365	ggccaggattcctctctca	2231	2250	SEQ ID NO: 5443	tgagccaccgcaccgggcc	2801	2820	1	3
SEQ ID NO: 5366	gccaactcctccttgctg	2493	2512	SEQ ID NO: 5444	caggctggagtgagtgcc	2555	2574	1	3
SEQ ID NO: 5367	tttttttcttttttgag	2519	2538	SEQ ID NO: 5445	ctcataacatctttgaaaa	2977	2996	1	3
SEQ ID NO: 5368	ccggcgtgcaccacctgc	2652	2671	SEQ ID NO: 5446	gcatgagccaccgcaccgg	2798	2817	1	3

Table 11. Selected palindromic sequences from rat glucose-6-phosphatase

Table 11: Selected pairwise sequence homology between rat glucose 6-phosphatase									
Source		Start Index	End Index	Match	Start Index	End Index	#	B	
SEQ ID NO:	5447ctgactattacagcaacag	301	320	SEQ ID NO:	5471ctgtggctgaaacttcag	598	617	1	6
SEQ ID NO:	5448ctcttgggggttggggctgg	831	850	SEQ ID NO:	5472ccagcatgtaccgcaagag	859	878	1	6
SEQ ID NO:	5449tgcaaaggagaactgcgca	879	898	SEQ ID NO:	5473tgcgaccgtccccttgca	1019	1038	1	6
SEQ ID NO:	5450cctcggggccatgccatggg	376	395	SEQ ID NO:	5474cccagtggtggggccagagg	1171	1190	1	5
SEQ ID NO:	5451ttgagcaaaccatatgcaa	1478	1497	SEQ ID NO:	5475ttgcagagtgtgtcttcaa	2057	2076	1	5
SEQ ID NO:	5452cagcttcctgaggtaccaa	2	21	SEQ ID NO:	5476ttgggtgtctgtgatcgctg	123	142	1	4
SEQ ID NO:	5453ggtaccaaggaggaaggat	13	32	SEQ ID NO:	5477atccagtgcactcgctacc	66	85	1	4
SEQ ID NO:	5454ctccacgactttgggatcc	51	70	SEQ ID NO:	5478ggatcgggaggaggggggag	1448	1467	1	4
SEQ ID NO:	5455caggactggtttgtcttgg	108	127	SEQ ID NO:	5479ccaagcccagctgtgcctg	2018	2037	1	4
SEQ ID NO:	5456cttctatgtcctcttccc	155	174	SEQ ID NO:	5480gggacagacacacaagaag	1076	1095	1	4
SEQ ID NO:	5457ttctatgtcctcttccca	156	175	SEQ ID NO:	5481tgggacagacacacaagaa	1075	1094	1	4
SEQ ID NO:	5458tggttccacattcaagaga	177	196	SEQ ID NO:	5482tctcaataatgatagacca	1549	1568	1	4
SEQ ID NO:	5459tgctctgataaaacagtt	325	344	SEQ ID NO:	5483aactctgagatcttgggca	1868	1887	1	4
SEQ ID NO:	5460agcccggctcctgggacag	1064	1083	SEQ ID NO:	5484ctgtcctccagcctgggct	2034	2053	1	4
SEQ ID NO:	5461agtcttgacacaagtcag	1111	1130	SEQ ID NO:	5485ctgaatggtaatggtgact	1659	1678	1	4
SEQ ID NO:	5462aaaaagggtgaatttttaa	1237	1256	SEQ ID NO:	5486tttattaaaacgacattt	2201	2220	1	4
SEQ ID NO:	5463acactctcaataatgatag	1545	1564	SEQ ID NO:	5487ctatgaatgatgcctgtgt	2121	2140	1	4
SEQ ID NO:	5464aaagaatgaacgtgctcca	37	56	SEQ ID NO:	5488tggacctcctgtggacttt	724	743	1	3
SEQ ID NO:	5465cttgggatccagtcgact	59	78	SEQ ID NO:	5489agtcagcggccgtgcaaag	1124	1143	1	3
SEQ ID NO:	5466gtgatcgctgacctcagga	132	151	SEQ ID NO:	5490tcctctctccaaagggtcac	1911	1930	1	3
SEQ ID NO:	5467ggaacgccttctatgtcct	148	167	SEQ ID NO:	5491aggactcatcactgcttcc	1748	1767	1	3
SEQ ID NO:	5468gactgtgggcatcaatctc	194	213	SEQ ID NO:	5492gagactggaccagggagtc	357	376	1	3
SEQ ID NO:	5469ggacactgactattacagc	296	315	SEQ ID NO:	5493gctgaacgtctgtctgtcc	518	537	1	3
SEQ ID NO:	5470aagcccccgctcccagattg	966	985	SEQ ID NO:	5494caattgtttgctgggtgctt	1833	1852	1	3

Table 12. Selected palindromic sequences from human B-catenin

Source	Start Index	End Index	Match	Start Index	End Index	#	B
SEQ ID NO: 5495 agcagcttcagtccecgcc	70	89	SEQ ID NO: 5542 ggcgacatatgcagctgct	2152	2171	1	5
SEQ ID NO: 5496 ccattctgggtgccactacc	304	323	SEQ ID NO: 5543 gggtatggaccccatgalgg	2387	2406	1	5
SEQ ID NO: 5497 tccttctctgagtggtaaa	328	347	SEQ ID NO: 5544 ttattacatcaagaagga	985	1004	1	5
SEQ ID NO: 5498 tctgagtggttaaaggcaat	334	353	SEQ ID NO: 5545 attgtacgtaccatgcaga	791	810	1	5
SEQ ID NO: 5499 cagaggggtacgagctgcta	473	492	SEQ ID NO: 5546 tagctgcaggggtcctctg	2037	2056	1	5
SEQ ID NO: 5500 ctaaatgacgaggaccagg	677	696	SEQ ID NO: 5547 cctgtaaatcatccttag	2539	2558	1	5
SEQ ID NO: 5501 taaatgacgaggaccagg	678	697	SEQ ID NO: 5548 acctgtaaatcatccttta	2538	2557	1	5
SEQ ID NO: 5502 gtctgtatgagtggaac	383	402	SEQ ID NO: 5549 gttccgaatgtctgaggac	2176	2195	2	4
SEQ ID NO: 5503 cccagcgccgtacgtccat	1839	1858	SEQ ID NO: 5550 atgggctgccagatctggg	2451	2470	2	4
SEQ ID NO: 5504 tcccctgaggggtatttgaa	143	162	SEQ ID NO: 5551 ticacatcctagctcggga	1929	1948	1	4
SEQ ID NO: 5505 ggggtattgaagtatacca	151	170	SEQ ID NO: 5552 tgggtaagctcttacaccc	1680	1699	1	4
SEQ ID NO: 5506 gctgttagtcactggcagc	260	279	SEQ ID NO: 5553 gctgcctccagggtgacagc	2494	2513	1	4
SEQ ID NO: 5507 gtctgtatgagtggaac	383	402	SEQ ID NO: 5554 gttcgcttcactatggac	1652	1671	1	4
SEQ ID NO: 5508 tcctgtatgagtggaaca	384	403	SEQ ID NO: 5555 tgttccgaatgtctgagga	2175	2194	1	4
SEQ ID NO: 5509 gtatgcaatgactcgagct	454	473	SEQ ID NO: 5556 agctggcctgggttgatac	2517	2536	1	4
SEQ ID NO: 5510 gtccagcggttggtgaac	563	582	SEQ ID NO: 5557 gttcgcttcactatggac	1652	1671	1	4
SEQ ID NO: 5511 tatcaagatgatgcagaac	623	642	SEQ ID NO: 5558 gttcgtgcacatcaggata	1820	1839	1	4
SEQ ID NO: 5512 tatgggtccatcagcttct	718	737	SEQ ID NO: 5559 agaaagcaagctcatcata	1126	1145	1	4
SEQ ID NO: 5513 ccctgggtgaaaatgcttgg	915	934	SEQ ID NO: 5560 ccaaagagtagctgcaggg	2029	2048	1	4
SEQ ID NO: 5514 agctttaggacttcacctg	1291	1310	SEQ ID NO: 5561 cagggtgacagcaatcagct	2502	2521	1	4
SEQ ID NO: 5515 ggaatcttcagatgctgc	1356	1375	SEQ ID NO: 5562 gcagctgctgtttgttcc	2162	2181	1	4
SEQ ID NO: 5516 tgccttcgggctgggtgac	1549	1568	SEQ ID NO: 5563 gtcatctgaccagccgaca	1605	1624	1	4
SEQ ID NO: 5517 cacagctcctctgacagag	2107	2126	SEQ ID NO: 5564 ctctaggaatgaagggtgtg	2134	2153	1	4
SEQ ID NO: 5518 ccagacagaaaagcggctg	245	264	SEQ ID NO: 5565 cagctcgtgtaccgctgg	828	847	2	3
SEQ ID NO: 5519 cagcagcgttggcccgcc	4	23	SEQ ID NO: 5566 ggccaccaccctgggtgctg	2420	2439	1	3
SEQ ID NO: 5520 aggtctgaggagcagcttc	60	79	SEQ ID NO: 5567 gaagaggatgtggatacct	359	378	1	3
SEQ ID NO: 5521 actgtttgaaaatccagc	174	193	SEQ ID NO: 5568 gctgatattgatggacagt	437	456	1	3
SEQ ID NO: 5522 ctgattgatggagtggga	213	232	SEQ ID NO: 5569 tccagggtgacagcaatcag	2500	2519	1	3
SEQ ID NO: 5523 ccagacagaaaagcggctg	245	264	SEQ ID NO: 5570 cagcaacagctctacctgg	275	294	1	3
SEQ ID NO: 5524 acagctccttctctgagtg	323	342	SEQ ID NO: 5571 cactgagcctgccatctgt	1579	1598	1	3
SEQ ID NO: 5525 tggatacctccaagtcct	369	388	SEQ ID NO: 5572 aggactaaataccattcca	1972	1991	1	3
SEQ ID NO: 5526 tcaagaacaagtagctgat	424	443	SEQ ID NO: 5573 atcagctggcctgggttga	2514	2533	1	3
SEQ ID NO: 5527 agctcagaggggtacgagct	469	488	SEQ ID NO: 5574 agctgggtggaatgcaagct	1276	1295	1	3
SEQ ID NO: 5528 gcatgcagatcccatctac	516	535	SEQ ID NO: 5575 gtagaagctgggtggaatgc	1271	1290	1	3
SEQ ID NO: 5529 ccacacgtgcaatccctga	645	664	SEQ ID NO: 5576 tcagatgatataaatgtgg	1430	1449	1	3
SEQ ID NO: 5530 cacacgtgcaatccctgaa	646	665	SEQ ID NO: 5577 ttcagatgatataaatgtg	1429	1448	1	3
SEQ ID NO: 5531 ggacctgcataacctttc	846	865	SEQ ID NO: 5578 gaaatcttgcccttgtcc	1743	1762	1	3
SEQ ID NO: 5532 ctccacaacctttattac	974	993	SEQ ID NO: 5579 gtaaatcatcctttaggag	2542	2561	1	3
SEQ ID NO: 5533 cagagtgtgaagggtgcta	1222	1241	SEQ ID NO: 5580 tagctgcaggggtcctctg	2037	2056	1	3
SEQ ID NO: 5534 ggactctcaggaatcttcc	1347	1366	SEQ ID NO: 5581 gaaatcttgcccttgtcc	1743	1762	1	3
SEQ ID NO: 5535 tgatataaatgtgggtcacc	1435	1454	SEQ ID NO: 5582 ggtgacaggggaagacatca	1562	1581	1	3
SEQ ID NO: 5536 cccagcgccgtacgtccat	1839	1858	SEQ ID NO: 5583 atggccaggatgccttggg	2370	2389	1	3
SEQ ID NO: 5537 gtccatgggtgggacacag	1852	1871	SEQ ID NO: 5584 ctgtgaacttgctcaggac	2053	2072	1	3
SEQ ID NO: 5538 ttgtaccggagcccttcac	1915	1934	SEQ ID NO: 5585 gtgaacttgctcaggacaa	2055	2074	1	3
SEQ ID NO: 5539 ttgtatcagaggactaaa	1962	1981	SEQ ID NO: 5586 tttaggagtaacaatacaa	2553	2572	1	3

SEQ ID NO:	5540	gaagctattgaagctgagg	2084	2103	SEQ ID NO:	5587	cctctgacagagtacttc	2114	2133	1	3
SEQ ID NO:	5541	tcagaacagagccaatggc	2247	2266	SEQ ID NO:	5588	gccaccaccctggtgctga	2421	2440	1	3



Table 13. Selected palindromic sequences from human hepatitis C virus (HCV)

	Source	Start Index	End Index		Match	Start Index	End Index	#	B
SEQ ID NO: 5589	cagcacctgggtgctggta	5314	5333	SEQ ID NO: 6135	taccatcaccagctgctg	6196	6215	1	9
SEQ ID NO: 5590	aactcgtccggatgcccg	1682	1701	SEQ ID NO: 6136	ccgggcagcgggtcgagtt	8202	8221	1	8
SEQ ID NO: 5591	cgctgctgggtagcgctca	1049	1068	SEQ ID NO: 6137	tgagagcgacgccgcagcg	6151	6170	1	7
SEQ ID NO: 5592	ctccggatcccacaagccg	1352	1371	SEQ ID NO: 6138	cggcattgtgggcccgggag	6053	6072	1	7
SEQ ID NO: 5593	tgtaacatcgggggggtcg	2048	2067	SEQ ID NO: 6139	cgaccctcccacattaca	6871	6890	1	7
SEQ ID NO: 5594	gtaacatcgggggggtcgg	2049	2068	SEQ ID NO: 6140	ccgaccctcccacattac	6870	6889	1	7
SEQ ID NO: 5595	cagccaccaagcaggcgga	5556	5575	SEQ ID NO: 6141	tccggctgggtcgttgctg	9254	9273	1	7
SEQ ID NO: 5596	ctcaccaccagaacaccc	5744	5763	SEQ ID NO: 6142	gggtgtgcacggtgttgag	6291	6310	1	7
SEQ ID NO: 5597	ccagccttaccatcaccca	6189	6208	SEQ ID NO: 6143	tgggcgctgggtatgcctgg	5832	5851	1	7
SEQ ID NO: 5598	ctacgcggtgtccggctc	6249	6268	SEQ ID NO: 6144	gagcccgaaccggacgtag	6830	6849	1	7
SEQ ID NO: 5599	tacgcggtgtccggctcg	6250	6269	SEQ ID NO: 6145	cgagcccgaaccggacgta	6829	6848	1	7
SEQ ID NO: 5600	gagttcctggtaaaagcct	8216	8235	SEQ ID NO: 6146	aggctatgactaggtactc	8634	8653	1	7
SEQ ID NO: 5601	atggcggggaactgggcta	1430	1449	SEQ ID NO: 6147	tagcgcattttcactccat	9019	9038	2	6
SEQ ID NO: 5602	aaccaaacgtaacaccaac	370	389	SEQ ID NO: 6148	gttgccgctaccttaggtt	4115	4134	1	6
SEQ ID NO: 5603	ggtggtcagatcgttggtg	419	438	SEQ ID NO: 6149	caccagcccgcctaccacc	5734	5753	1	6
SEQ ID NO: 5604	cctggcccctctatggca	584	603	SEQ ID NO: 6150	tgccaacgtgggtacaagg	6374	6393	1	6
SEQ ID NO: 5605	taccccgccacgcgtcag	1265	1284	SEQ ID NO: 6151	ctgacgactagctgcggta	8465	8484	1	6
SEQ ID NO: 5606	gggcacgctgccgcctca	1508	1527	SEQ ID NO: 6152	tgagacgacgaccgtgcc	4759	4778	1	6
SEQ ID NO: 5607	ctgcaatgactccctccag	1624	1643	SEQ ID NO: 6153	ctggtggccctcaatgcag	2594	2613	1	6
SEQ ID NO: 5608	aaccgatcgtctcggaac	1897	1916	SEQ ID NO: 6154	gttgccgctaccttaggtt	4115	4134	1	6
SEQ ID NO: 5609	gtgcggggcccccccggtg	2032	2051	SEQ ID NO: 6155	acaccacgggccccctgcac	6537	6556	1	6
SEQ ID NO: 5610	atgtggggggcggtggagca	2238	2257	SEQ ID NO: 6156	tgctcaatgtcctacacat	7610	7629	1	6
SEQ ID NO: 5611	ggagagcggtgcaacttg	2288	2307	SEQ ID NO: 6157	ccaagctcaaactcactcc	9207	9226	1	6
SEQ ID NO: 5612	cgtccgttgccggagcgca	2613	2632	SEQ ID NO: 6158	tgagagcccgaaccggacg	6827	6846	1	6
SEQ ID NO: 5613	gtctggcattatgacctt	2817	2836	SEQ ID NO: 6159	aaggtcaccttgacagac	7763	7782	1	6
SEQ ID NO: 5614	tcttgatatcaccaaact	2997	3016	SEQ ID NO: 6160	agttcgatgaaatggaaga	5454	5473	1	6
SEQ ID NO: 5615	cttctgattgccatactcg	3014	3033	SEQ ID NO: 6161	cgagcaattcaagcagaag	5518	5537	1	6
SEQ ID NO: 5616	gcggcggtgtgggacatca	3314	3333	SEQ ID NO: 6162	tgatcacgccatgcgccgc	7641	7660	1	6
SEQ ID NO: 5617	gggacatcatcctgggcct	3324	3343	SEQ ID NO: 6163	aggcggtggattttgtccc	3915	3934	1	6
SEQ ID NO: 5618	gggcgtcttcggggccgct	3874	3893	SEQ ID NO: 6164	agcggcacggcgaccgccc	7439	7458	1	6
SEQ ID NO: 5619	ggcgtcttcggggccgctg	3875	3894	SEQ ID NO: 6165	cagcggcacggcgaccgccc	7438	7457	1	6
SEQ ID NO: 5620	gcgtcttcggggccgctgt	3876	3895	SEQ ID NO: 6166	acaggtgccctgatcacgc	7631	7650	1	6
SEQ ID NO: 5621	gtccccgggtcttcacagac	3961	3980	SEQ ID NO: 6167	gtcttgaagaaccgggac	7252	7271	1	6
SEQ ID NO: 5622	catcaggactggggttaagg	4174	4193	SEQ ID NO: 6168	ccctctcaagccgtgatg	8155	8174	1	6
SEQ ID NO: 5623	ccgacgggtggttgctccg	4245	4264	SEQ ID NO: 6169	ccgggggaacggccctcgg	4853	4872	1	6
SEQ ID NO: 5624	ggggggaaggcacctcatt	4501	4520	SEQ ID NO: 6170	aatgtgtgacttggcccc	8334	8353	1	6
SEQ ID NO: 5625	ccgagcaattcaagcagaa	5517	5536	SEQ ID NO: 6171	ttctgattgccatactcg	3015	3034	1	6
SEQ ID NO: 5626	agatgaaggcaaaggcgtc	7821	7840	SEQ ID NO: 6172	gacgacctgtcgttatct	8564	8583	1	6
SEQ ID NO: 5627	cccctagggggcgctgcca	767	786	SEQ ID NO: 6173	tggccggcgccccccgggg	3674	3693	3	5
SEQ ID NO: 5628	ctcccgccctagtggggc	646	665	SEQ ID NO: 6174	gcccccccttgagggggag	7519	7538	2	5
SEQ ID NO: 5629	ttccgctcgtcggcgcc	750	769	SEQ ID NO: 6175	gggcaaaggacgtccggaa	7923	7942	2	5
SEQ ID NO: 5630	cccctagggggcgctgcca	767	786	SEQ ID NO: 6176	tggcggggggccactgggg	1383	1402	2	5
SEQ ID NO: 5631	gccccgcccgcgtgcgaca	1222	1241	SEQ ID NO: 6177	tgtcccagggggggaggggc	9147	9166	2	5

SEQ ID NO: 5632	aggacgaccgggtccttct	178	197	SEQ ID NO: 6178	gaaaaaggacgggtgtcct	7341	7360	1	5
SEQ ID NO: 5633	ggacgaccgggtccttct	179	198	SEQ ID NO: 6179	agaaaaaggacgggtgtcc	7340	7359	1	5
SEQ ID NO: 5634	aaaaccaaacgtaacacca	368	387	SEQ ID NO: 6180	tggttttttttttttt	9443	9462	1	5
SEQ ID NO: 5635	caaccgcccacaggac	385	404	SEQ ID NO: 6181	gtcctgaaccgctgttg	4100	4119	1	5
SEQ ID NO: 5636	cgggtggcagatcgttgg	418	437	SEQ ID NO: 6182	accatlgagacgacgaccg	4754	4773	1	5
SEQ ID NO: 5637	acctgtgccgcgagggg	444	463	SEQ ID NO: 6183	ccccggccacgctcagg	1267	1286	1	5
SEQ ID NO: 5638	tggcgcgaggggccccag	450	469	SEQ ID NO: 6184	ctgggcgcgctgacgggca	3164	3183	1	5
SEQ ID NO: 5639	gggccccagggtgggtgtg	460	479	SEQ ID NO: 6185	cacagcctgtctcgtgccc	9296	9315	1	5
SEQ ID NO: 5640	gttggggccccacggaccc	657	676	SEQ ID NO: 6186	gggtgggtagccgccaac	5783	5802	1	5
SEQ ID NO: 5641	ttggggccccacggacccc	658	677	SEQ ID NO: 6187	ggggtgggtagccgccaac	5782	5801	1	5
SEQ ID NO: 5642	tggggccccacggaccccc	659	678	SEQ ID NO: 6188	gggggtgggtagccgcca	5781	5800	1	5
SEQ ID NO: 5643	cctcacatgcggcctcgcc	715	734	SEQ ID NO: 6189	ggcggggcgacaatagagg	3774	3793	1	5
SEQ ID NO: 5644	cacatgcggcctcgccgac	718	737	SEQ ID NO: 6190	gtcgtcggagtcgtgtgtg	6020	6039	1	5
SEQ ID NO: 5645	tccgctcgtcggcgccccc	751	770	SEQ ID NO: 6191	ggggcaaaggacgtccgga	7922	7941	1	5
SEQ ID NO: 5646	ggcgcgcagggccttgg	776	795	SEQ ID NO: 6192	ccaagccacagtgtgcgcc	5110	5129	1	5
SEQ ID NO: 5647	ccatgtcacgaacgactgc	943	962	SEQ ID NO: 6193	gcagcaacacgtggcatgg	6498	6517	1	5
SEQ ID NO: 5648	gtgccctgcgttcgggagg	1019	1038	SEQ ID NO: 6194	cctcacaacggggggggcac	1495	1514	1	5
SEQ ID NO: 5649	tgcctgcgttcgggagg	1020	1039	SEQ ID NO: 6195	ccctcacaacggggggggca	1494	1513	1	5
SEQ ID NO: 5650	gccctgcgttcgggagggt	1021	1040	SEQ ID NO: 6196	accctcacaacggggggggc	1493	1512	1	5
SEQ ID NO: 5651	aggaatgctaccatcccca	1085	1104	SEQ ID NO: 6197	tgggcatcgccacagtcct	4323	4342	1	5
SEQ ID NO: 5652	tccccactacgacaatacg	1098	1117	SEQ ID NO: 6198	cgtattcccagatttggga	8092	8111	1	5
SEQ ID NO: 5653	atacgacaccacgtcgatt	1112	1131	SEQ ID NO: 6199	aatcaatgctgtagcgtat	4576	4595	1	5
SEQ ID NO: 5654	atttgctcgttggggcggc	1128	1147	SEQ ID NO: 6200	gccgccacttgcggcaaat	9164	9183	1	5
SEQ ID NO: 5655	ccttctcgccccgccggca	1215	1234	SEQ ID NO: 6201	tgccaacgtgggtacaagg	6374	6393	1	5
SEQ ID NO: 5656	acccggccacgcgtcagg	1266	1285	SEQ ID NO: 6202	cctgccgcggttaccgggt	6340	6359	1	5
SEQ ID NO: 5657	gccctcgtagtgtgcag	1331	1350	SEQ ID NO: 6203	actgcgtcggcatgtgggc	6046	6065	1	5
SEQ ID NO: 5658	gccgtctcagagaatccag	1558	1577	SEQ ID NO: 6204	ctggtatcgttgtgcggc	5838	5857	1	5
SEQ ID NO: 5659	ctgaactgcaatgactccc	1619	1638	SEQ ID NO: 6205	gggacagatcggagctcag	2313	2332	1	5
SEQ ID NO: 5660	agactgggttcttgcgc	1641	1660	SEQ ID NO: 6206	gcggcgagcctacgagtct	8609	8628	1	5
SEQ ID NO: 5661	tgtccggatgcccgagc	1685	1704	SEQ ID NO: 6207	gtccgggggcgcttacga	4257	4276	1	5
SEQ ID NO: 5662	ccagggatggggctctatc	1738	1757	SEQ ID NO: 6208	gataacttcccctacctgg	5084	5103	1	5
SEQ ID NO: 5663	gacaaccgatcgtctcggc	1894	1913	SEQ ID NO: 6209	gccgcggttaccgggtgtc	6343	6362	1	5
SEQ ID NO: 5664	caagacgtgcggggccccc	2026	2045	SEQ ID NO: 6210	gggggtctccccctcttg	6919	6938	1	5
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SEQ ID NO: 6131	agttcgtgtatgcgagaag	8110	8129	SEQ ID NO: 6677	cttcatgcctcaggaaact	9069	9088	1	3
SEQ ID NO: 6132	ggctataaaatcgctcaca	8365	8384	SEQ ID NO: 6678	tgtgaaagggtccgtgagcc	9551	9570	1	3
SEQ ID NO: 6133	ttctccatccttctagctc	8900	8919	SEQ ID NO: 6679	gagcggagggggatgagaa	7134	7153	1	3
SEQ ID NO: 6134	tgtctcgtgcccgaccccg	9303	9322	SEQ ID NO: 6680	cggggcgcgttcctgaca	3688	3707	1	3



Table 14. Sequences from human hepatitis C virus (HCV) (Direct Match Type)

	Source	Start Index	End Index		Match	Start Index	End Index	Match #
SEQ ID NO: 6755	tttttttttttttttttt	9446	9465	SEQ ID NO:6758	tttttttttttttttttt	9466	9485	2
SEQ ID NO: 6756	tttttttttttttttttt	9446	9465	SEQ ID NO:6759	tttttttttttttttttt	9465	9484	1
SEQ ID NO: 6757	tttttttttttttttttt	9447	9466	SEQ ID NO:6760	tttttttttttttttttt	9466	9485	1

5     **Table 15. Sequences of Exemplary Gene Targets**

gi|4502152|ref|NM\_000384.1| Homo sapiens apolipoprotein B (including Ag(x) antigen) (APOB), mRNA

ATTCCCACCGGGACCTGCGGGGCTGAGTGCCCTTCTCGGTTGCTGCCGCTGAGGAGCCCCGCCAGCCAGC  
CAGGGCCGCGAGGCCGAGGCCAGGCCGCAGCCAGGAGCCGCCCCACCGCAGCTGGCGATGGACCCGCCG  
10 AGGCCCCGCGCTGCTGGCGCTGCTGGCGCTGCCTGCGCTGCTGCTGCTGCTGGCGGGCGCCAGGGCCG  
AAGAGGAAATGCTGGAAAATGTCAGCCTGGTCTGTCCAAAAGATGCGACCCGATTCAAGCACCTCCGGAA  
GTACACATACAACTATGAGGCTGAGAGTTCAGTGAGTCCCTGGGACTGCTGATTCAAGAAGTGCCACC  
AGGATCAACTGCAAGGTTGAGCTGGAGGTTCCCCAGCTCTGCAGCTTCATCCTGAAGACCAGCCAGTGCA  
CCCTGAAAGAGGTGTATGGCTTCAACCCTGAGGGCAAAGCCTTGCTGAAGAAAACCAAGAAGTCTGAGGA  
15 GTTTGCTGCAGCCATGTCCAGGTATGAGCTCAAGCTGGCCATTCCAGAAGGGAAGCAGGTTTTCTTTTAC  
CCGGAGAAAGATGAACCTACTTACATCCTGAACATCAAGAGGGGCATCATTTCTGCCCTCCTGGTTCCCC  
CAGAGACAGAAGAAGCCAAGCAAGTGTTGTTTCTGGATACCGTGTATGGAACTGCTCCACTCACTTTTAC  
CGTCAAGACGAGGAAGGGCAATGTGGCAACAGAAATATCCACTGAAAGAGACCTGGGGCAGTGTGATCGC  
TTCAAGCCCATCCGCACAGGCATCAGCCCACTTGCTCTCATCAAAGGCATGACCCGCCCTTGTTCAACTC  
20 TGATCAGCAGCAGCCAGTCCTGTCAGTACACACTGGACGCTAAGAGGAAGCATGTGGCAGAAGCCATCTG  
CAAGGAGCAACACCTCTTCTGCTTTCTCCTACAACAATAAGTATGGGATGGTAGCACAAGTGACACAG  
ACTTTGAACTTGAAGACACACCAAAGATCAACAGCCGCTTCTTTGGTGAAGGTACTAAGAAGATGGGCC  
TCGCATTTGAGAGCACCAAATCCACATCACCTCCAAAGCAGGCCGAAGCTGTTTTGAAGACTCTCCAGGA  
ACTGAAAAAACTAACCATCTCTGAGCAAAATATCCAGAGAGCTAATCTCTTCAATAAGCTGGTTACTGAG  
25 CTGAGAGGCCCTCAGTGATGAAGCAGTCACATCTCTTGGCCACAGCTGATTGAGGTGTCCAGCCCCATCA  
CTTTACAAGCCTTGTTTCAGTGTGGACAGCCTCAGTGCTCCACTCACATCCTCCAGTGGCTGAAACGTGT  
GCATGCCAACCCCTTCTGATAGATGTGGTCACCTACCTGGTGGCCCTGATCCCCGAGCCCTCAGCACAG  
CAGCTGCGAGAGATCTTCAACATGGCGAGGGATCAGCGCAGCCGAGCCACCTTGTATGCGCTGAGCCACG  
CGGTCAACAACTATCATAAGACAAACCTACAGGGACCCAGGAGCTGCTGGACATTGCTAATTACCTGAT  
30 GGAACAGATTCAAGATGACTGCACTGGGGATGAAGATTACACCTATTTGATTCTGCGGGTCATTGGAAAT  
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35 AAGTGAAGAACTTTGTGGCTTCCCATATTGCCAATATCTTGAACCTCAGAAGAATTGGATATCCAAGATCT  
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ATTTGCTTCAGCTGACCTCATCGAGATTGGCTTGAAGGAAAAGGCTTTGAGCCAACATTGGAAGCTCTT  
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TCCGGACTTCGCTAGGAGTGGGGTCCAGATGAACACCAACTTCTTCCACGAGTCGGGTCTGGAGGCTCAT  
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5 GAGGCAACACATTACATTTGGTCTCTACCACCAAAACGGAGGTGATCCCACCTCTCATTGAGAACAGGCA  
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>gi|4557442|ref|NM\_000078.1| Homo sapiens cholesteryl ester transfer  
protein, plasma (CETP), mRNA

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25

>gi|414668|emb|X75500.1|HSMTP H.sapiens mRNA for microsomal triglyceride  
transfer protein  
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>gi|1217638|emb|X91148.1|HSMTP H.sapiens mRNA for microsomal triglyceride  
transfer protein  
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20 AATATGAAATAAGGAGAAAAATGTTTTTATTTGTATGAATTAAGATCCATGTTGAACATTTGCAAATA  
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25

>gi|21361125|ref|NM\_001467.2| Homo sapiens glucose-6-phosphatase,  
transport (glucose-6-phosphate) protein 1 (G6PT1), mRNA  
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40 CAGCAGCCAGTCGGCAGCTTATGCTATCAGCAAGTTTGTGAGTGGGGTGCTGTCTGACCAGATGAGTGCT  
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10

gi|4503130|ref|NM\_001904.1| Homo sapiens catenin (cadherin-associated  
 protein), beta 1, 88kDa (CTNBN1), mRNA  
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TT (SEQ ID NO:6686)

10 gi|18104977|ref|NM\_002827.2| Homo sapiens protein tyrosine phosphatase,  
non-receptor type 1 (PTPN1), mRNA  
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30 AGCATGAGTCAAGACACTGAAGTTAGAAGTCGGGTCTGTTGGGGGGAAGTCTTCGAGGTGCCAGGCTGCCT  
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35 GTTGGTTCTGCACTAAAACCCATCTTCCCCGGATGTGTGTCTCACCCCTCATCCTTTTACTTTTTGCCCC  
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5

gi|12831192|gb|AF333324.1| Hepatitis C virus type 1b polyprotein mRNA,  
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(SEQ ID NO:6688)

35

gi|306286|gb|M96362.1|HPCUNKCDS Hepatitis C virus mRNA, complete cds  
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gi|329739|gb|L02836.1|HPCCGENOM Hepatitis C China virus complete genome

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55 (SEQ ID NO: 6691)



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(SEQ ID NO: 6692)

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gi|339549|gb|M19154.1|HUMTGFB2A Human transforming growth factor-beta-2 mRNA, complete cds

35 GCCCCTCCCGTCAGTTCGCCAGCTGCCAGCCCCGGGACCTTTTCATCTCTTCCCTTTTGGCCGGAGGAGC  
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15 GAGAAAGTCTGCATTAAGATAAAGACCCTGAAAACACATGTTATGTATCAGCTGCCTAAGGAAGCTTCTT  
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gi|186624|gb|J04111.1|HUMJUNA Human c-jun proto oncogene (JUN), complete cds, clone hCJ-1

20 CCCGGGGAGGGGACCGGGGAACAGAGGGCCGAGAGGCGTGCGGCAGGGGGGAGGGTAGGAGAAAGAAGGG  
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25 GGGCTCAGAGTTGCACTGAGTGTGGCTGAAGCAGCGAGGCGGGAGTGGAGGTGCGCGGAGTCAAGCAGAC  
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35 GCTCAGTGAGTGACCGCGACTTTTCAAAGCCGGGTAGCGCGCGCAGTGCACAAGTAAGAGTGCGGGAGG  
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45 GGCATGGTGGCTCCCGCGGTAGCCTCGGTGGCAGGGGGCAGCGGCAGCGGCGGCTTCAGCGCCAGCCTGC  
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55 CCAAGTTGGACTGGGTTTCGGTCTGACGGCGCCCCCAGTGTGCACGAGTGGGAAGGACTTGGTTCGCGCCCT

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5 ACAGATGAACCTTTCTGGCCTGCTTTCGTTAACTGTGTATGTACATATATATATTTTTTAATTTGATTA  
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TAACAGCATTTCTGTCACAATAAATGTATTCAAATACCAATAACAGATCTTGAATTGCTTCCCTTTACTAC  
TTTTTTGTTCCCAAGTTATATACTGAAGTTTTTATTTTTTAGTTGCTGAGGTT (SEQ ID NO:6695)

20 gi|179982|gb|M57729.1|HUMCCC5 Human complement component C5 mRNA, complete  
cds  
CTACCTCCAACCATGGGCCTTTTGGGAATACTTTGTTTTTTAATCTTCCTGGGGAAAACCTGGGGACAGG  
AGCAAACATATGTCATTTTCAGCACCAAAAATATTTCCGTGTTGGAGCATCTGAAAATATTGTGATTCAAGT  
TTATGGATACACTGAAGCATTGATGCAACAATCTCTATTAAAAGTTATCCTGATAAAAAATTTAGTTAC  
25 TCCTCAGGCCATGTTTCATTTATCCTCAGAGAATAAATTCCAAAACCTCTGCAATCTTAACAATACAACCAA  
AACAAATTGCCTGGAGGACAAAACCCAGTTTCTTATGTGTATTTGGAAGTTGTATCAAAGCATTTTTTCAA  
ATCAAAAAGAATGCCAATAACCTATGACAATGGATTTCTCTTCATTCATACAGACAAACCTGTTTATACT  
CCAGACCAGTCAGTAAAAGTTAGAGTTTATTCGTTGAATGACGACTTGAAGCCAGCCAAAAGAGAACTG  
TCTTAACCTTCATAGATCCTGAAGGATCAGAAGTTGACATGGTAGAAGAAATTGATCATATTGGAATTAT  
30 CTCTTTTCCTGACTTCAAGATTCCGTCTAATCCTAGATATGGTATGTGGACGATCAAGGCTAAATATAAA  
GAGGACTTTTCAACAACCTGGAACCGCATATTTTGAAGTTAAAGAATATGTCTTGCCACATTTTTCTGTCT  
CAATCGAGCCAGAATATAATTTCAATTGGTTACAAGAACTTTAAGAATTTTGAAATTACTATAAAAGCAAG  
ATATTTTTTATAATAAAGTAGTCACTGAGGCTGACGTTTATATCACATTTGGAATAAGAGAAGACTTAAAA  
GATGATCAAAAAGAAATGATGCAAAACAGCAATGCAAAAACAAATGTTGATAAATGGAATTGCTCAAGTCA  
35 CATTTGATTCTGAAACAGCAGTCAAAGAAGTGTCACTACTACAGTTTAGAAGATTTAAACAACAAGTACCT  
TTATATTGCTGTAACAGTCATAGAGTCTACAGGTGGATTTTCTGAAGAGGCAGAAATACCTGGCATCAAA  
TATGTCCTCTCTCCCTACAAACTGAATTTGGTTGCTACTCCTCTTTTCTGAAGCCTGGGATTCCATATC  
CCATCAAGGTGCAGGTTAAAGATTGCTTGACCAGTTGGTAGGAGGAGTCCCAGTAATACTGAATGCACA  
AACAATTGATGTAAACCAAGAGACATCTGACTTGGATCCAAGCAAAAGTGTAACACGTGTTGATGATGGA  
40 GTAGCTTCCTTTGTGCTTAATCTCCCATCTGGAGTGACGGTGCTGGAGTTTAATGTCAAAACTGATGCTC  
CAGATCTTCCAGAAGAAAATCAGGCCAGGGAAGGTTACCGAGCAATAGCATACTCATCTCTCAGCCAAAG  
TTACCTTTTATATTGATTGGACTGATAACCATAAGGCTTTGCTAGTGGGAGAACATCTGAATATTATTGTT  
ACCCCCAAAAGCCCATATATTGACAAAATAACTCACTATAATTACTTGATTTTATCCAAGGGCAAATTA  
TCCATTTTGGCACGAGGGAGAAATTTTCAGATGCATCTTATCAAAGTATAAACATTCCAGTAACACAGAA  
45 CATGGTTCCTTCATCCCGACTTCTGGTCTATTATATCGTCACAGGAGAACAGACAGCAGAATTAGTGTCT  
GATTCACTGCTGGTTAAATATTGAAGAAAAATGTGGCAACCAGCTCCAGGTTTCATCTGTCTCCTGATGCAG  
ATGCATATTCTCCAGGCCAAACTGTGTCTCTTAATATGGCAACTGGAATGGATTCCTGGGTGGCATTAGC  
AGCAGTGGACAGTGTGTGTATGGAGTCAAAGAGGAGCCAAAAGCCCTTGGAAGAGTATTTCAATTC  
TTAGAGAAGAGTGATCTGGGCTGTGGGGCAGGTGGTGGCCTCAACAATGCCAATGTGTTCCACCTAGCTG  
50 GACTTACCTTCCTCACTAATGCAAATGCAGATGACTCCCAAGAAAATGATGAACCTTGTAAGAAATTCT  
CAGGCCAAGAAGAAGCTGCAAAAGAAGATAGAAGAAATAGCTGCTAAATATAAACATTCAGTAGTGAAG  
AAATGTTGTTACGATGGAGCCTGCGTTAATAATGATGAAACCTGTGAGCAGCGAGCTGCACGGATTAGTT  
TAGGGCCAAGATGCATCAAAGCTTTCAC'TGAATGTTGTGTCGTCGCAAGCCAGCTCCGTGCTAATATCTC  
TCATAAAGACATGCAATTGGGAAGGCTACACATGAAGACCCTGTTACCAGTAAGCAAGCCAGAAATTCGG  
55 AGTTATTTTCCAGAAGCTGGTTGTGGGAAGTTCATCTTGTTCCTCAGAAGAAAACAGTTGCAGTTTGCCC



TACCTGATTCTCTAACCACCTGGGAAATTCAAGGCATTGGCATTTCAAACACTGGTATATGTGTTGCTGA  
TACTGTCAAGGCCAAAGGTGTTCAAAGATGTCTTCCCTGGAAATGAATATACCATATTCTGTTGTACGAGGA  
GAACAGATCCAATTGAAAGGAACTGTTTACAACCTATAGGACTTCTGGGATGCAGTTCTGTGTTAAAATGT  
CTGCTGTGGAGGGAATCTGCACTTCGGAAAGCCCAGTCATTGATCATCAGGGGCACAAAGTCCTCCAAATG  
5 TGTGCGCCAGAAAGTAGAGGGCTCCTCCAGTCACCTTGGTGACATTCACTGTGCTTCCTCTGGAAATTGGC  
CTTCACAACATCAATTTTTTCACTGGAGACTTGGTTTGGAAAAGAAATCTTAGTAAAAACATTACGAGTGG  
TGCCAGAAGGTGTCAAAGGGGAAAGCTATTCTGGTGTACTTTGGATCCTAGGGGTATTTATGGTACCAT  
TAGCAGACGAAAGGAGTTCCCATACAGGATACCCTTAGATTTGGTCCCCAAAACAGAAATCAAAGGATT  
TTGAGTGTAAGGACTGCTTGTAGGTGAGATCTTGTCTGCAGTTCTAAGTCAGGAAGGCATCAATATCC  
10 TAACCCACCTCCCCAAAGGGAGTGCAGAGGCGGAGCTGATGAGCGTTGTCCAGTATTCTATGTTTTTCA  
CTACCTGGAAACAGGAAATCATTGGAACATTTTTTCACTTCTGACCCATTAATTGAAAAGCAGAACTGAAG  
AAAAAATTAAAAGAAGGGATGTTGAGCATTATGTCCTACAGAAATGCTGACTACTCTTACAGTGTGTGGA  
AGGGTGGAAAGTGCTAGCACTTGGTTAACAGCTTTTGCTTTAAGAGTACTTGGACAAGTAAATAAATACGT  
AGAGCAGAACCAAAATTCAATTTGTAATTCCTTTATTGTGGCTAGTTGAGAATTATCAATTAGATAATGGA  
15 TCTTTCAAGGAAAATTACAGTATCAACCAATAAAATTACAGGGTACCTTGCCTGTTGAAGCCCGAGAGA  
ACAGCTTATATCTTACAGCCTTTACTGTGATTGGAATTAGAAAGGCTTTCGATATATGCCCCCTGGTGAA  
AATCGACACAGCTCTAATTAAAGCTGACAACCTTTCTGCTTGAAAATACACTGCCAGCCCAGAGCACCTTT  
ACATTGGCCATTTCTGCGTATGCTCTTTCCCTGGGAGATAAAACTCACCCACAGTTTCGTTCAATTGTTT  
CAGCTTTGAAGAGAGAAGCTTTGGTTAAAGGTAATCCACCCATTTATCGTTTTTGGAAAGACAATCTTCA  
20 GCATAAAGACAGCTCTGTACCTAACACTGGTACGGCACGTATGGTAGAAACAACCTGCCTATGCTTTACTC  
ACCAGTCTGAACTTGAAAGATATAAATTATGTTAACCAGTCATCAAATGGCTATCAGAAGAGCAGAGGT  
ATGGAGGTGGCTTTTATTCAACCCAGGACACCATCAATGCCATTGAGGGCCTGACGGAATATTTACTCCT  
GGTTAAACAACCTCCGCTTGAGTATGGACATCGATGTTTCTTACAAGCATAAAGGTGCCTTACATAATTAT  
AAAATGACAGACAAGAATTTCTTGGGAGGCCAGTAGAGGTGCTTCTCAATGATGACCTCATTGTCAGTA  
25 CAGGATTTGGCAGTGGCTTGGCTACAGTACATGTAACAACCTGTAGTTCACAAAACCAGTACCTCTGAGGA  
AGTTTGCAGCTTTTATTTGAAAATCGATACTCAGGATATTGAAGCATCCCCTACAGAGGCTACGGAAAC  
TCTGATTACAAACGCATAGTAGCATGTGCCAGCTACAAGCCCAGCAGGGAAGAATCATCATCTGGATCCT  
CTCATGCGGTGATGGACATCTCCTTGCTTACTGGAATCAGTGCAAATGAAGAAGACTTAAAAGCCCTTGT  
GGAAGGGGTGGATCAACTATTTACTGATTACCAAATCAAAGATGGACATGTTATTCTGCAACTGAATTCTG  
30 ATTCCTCCAGTGATTTCTTTGTGTACGATTCCGGATATTTGAACTCTTTGAAGTTGGGTTTCTCAGTC  
CTGCCACTTTTACAGTTTACGAATACCACAGACCAGATAAACAGTGTACCATGTTTTATAGCACTTCCAA  
TATCAAAATTCAGAAAGTCTGTGAAGGAGCCGCGTGCAAGTGTGTAGAAGCTGATTGTGGGCAAATGCAG  
GAAGAATTGGATCTGACAATCTCTGCAGAGACAAGAAAACAAACAGCATGTAAACCAGAGATTGCATATG  
CTTATAAAGTTAGCATCACATCCATCACTGTAGAAAATGTTTTTGTCAAGTACAAGGCAACCCTTCTGGA  
35 TATCTACAAAACCTGGGGAAGCTGTTGCTGAGAAAGACTCTGAGATTACCTTCATTAAAAAGGTAACCTGT  
ACTAACGCTGAGCTGGTAAAAGGAAGACAGTACTTAATTATGGGTAAAGAAGCCCTCCAGATAAAATACA  
ATTTCAAGTTTCAGGTACATCTACCCTTTAGATTCCTTGACCTGGATTGAATACTGGCCTAGAGACACAAC  
ATGTTTCATCGTGTCAAGCATTTTATAGCTAATTTAGATGAATTTGCCGAAGATATCTTTTTAAATGGATGC  
TAAAATTCCTGAAGTTCAGCTGCATACAGTTTGCACCTTATGGACTCCTGTTGTTGAAGTTCTGTTTTTTG  
40 TTTTCTTCTTTTTTTTAAACATTCATAGCTGGTCTTATTTGTAAAGCTCACTTTACTTAGAATTAGTGGCA  
CTTGCTTTTTATTAGAGAATGATTTCAAATGCTGTAACTTTCTGAAATAACATGGCCTTGGAGGGCATGAA  
GACAGATACTCCTCCAAGGTTATTGGACACCGGAAACAATAAATTGGAACACCTCCTCAAACCTACCACT  
CAGGAATGTTTGCTGGGGCCGAAAGAACAGTCCATTGAAAGGGAGTATTACAAAAACATGGCCTTTGCTT  
GAAAGAAAATACCAAGGAACAGGAAACTGATCATTAAAGCCTGAGTTTGCTTTC (SEQ ID NO:6696)  
45

gi|189944|gb|L05144.1|HUMPHOCAR Homo sapiens (clone lamda-hPEC-3)  
phosphoenolpyruvate carboxykinase (PCK1) mRNA, complete cds  
TGGGAACACAACTTGCTGGCGGGAAGAGCCCGGAAAGAAACCTGTGGATCTCCCTTCGAGATCATCCAA  
50 AGAGAAGAAAGGTGACCTCACATTCGTGCCCCCTTAGCAGCACTCTGCAGAAATGCCTCCTCAGCTGCAAA  
ACGGCCTGAACCTCTCGGCCAAAGTTGTCCAGGGGAAGCCTGGACAGCCTGCCCCAGGCAGTGAGGGAGTT  
TCTCGAGAATAACGCTGAGCTGTGTGACGCTGATCACATCCACATCTGTGACGGCTCTGAGGAGGAGAAT  
GGGCGGCTTCTGGGCCAGATGGAGGAAGAGGGCATCCTCAGGCGGCTGAAGAAGTATGACAACTGCTGGT  
TGGCTCTCACTGACCCCAAGGATGTGGCCAGGATCGAAAGCAAGACGGTTATCGTCACCCAAGAGCAAAG  
55 AGACACAGTGCCCATCCCCAAAACAGGCCTCAGCCAGCTCGGTGCTGGATGTCAGAGGAGGATTTTGAG



AAAGCGTTCAATGCCAGGTTCCCAGGGTGCATGAAAGGTGCGACCATGTACGTCATCCCATTTCAGCATGG  
GGCCGCTGGGCTCACCTCTGTCTGAAGATCGGCATCGAGCTGACGGATTTCGCCCTACGTGGTGGCCAGCAT  
GCGGATCATGACGCGGATGGGCACGCCCGTCTTGAAGCACTGGGCGATGGGGAGTTTGTCAAATGCCTC  
CATTCTGTGGGGTGCCCTCTGCCTTTACAAAAGCCTTTGGTCAACAACCTGGCCCTGCAACCCGGAGCTGA  
5 CGCTCATCGCCACCTGCCTGACCGCAGAGAGATCATCTCCTTTGGCAGTGGGTACGGCGGGAACCTCGCT  
GCTCGGGAAGAAGTGCTTTGCTCTCAGGATGGCCAGCCGGCTGGCAGAGGAGGAAGGGTGGCTGGCAGAG  
CACATGCTGATTCTGGGTATAACCAACCCTGAGGGTGAGAAGAAGTACCTGGCGGCCGCATTTCCCAGCG  
CCTGCGGGAAGACCAACCTGGCCATGATGAACCCCAAGCCTCCCCGGGTGGAAGGTTGAGTGCCTCGGGGA  
TGACATTGCCTGGATGAAGTTTGACGCACAAGGTCATTTAAGGGCCATCAACCCAGAAAATGGCTTTTTTC  
10 GGTGTCTGCTCCTGGGACTTCAGTGAAGACCAACCCCAATGCCATCAAGACCATCCAGAAGAACACAATCT  
TTACCAATGTGGCCGAGACCAGCGACGGGGGCGTTTACTGGGAAGGCATTGATGAGCCGCTAGCTTCAGG  
CGTCACCATCACGTCTTGAAGAATAAGGAGTGGAGCTCAGAGGATGGGGAACCTTGTGCCCAACCCCAAC  
TCGAGGTTCTGCACCCCTGCCAGCCAGTGCCCCATCATTGATGCTGCCTGGGAGTCTCCGGAAGGTGTTT  
CCATTGAAGGCATTATCTTTGGAGGCCGTAGACCTGCTGGTGTCCCTCTAGTCTATGAAGCTCTCAGCTG  
15 GCAACATGGAGTCTTTGTGGGGGCGGCCATGAGATCAGAGGCCACAGCGGCTGCAGAACATAAAGGCAAA  
ATCATCATGCATGACCCCTTTGCCATGCGGCCCTTCTTTGGCTACAACCTTCGGCAAATACCTGGCCCACT  
GGCTTAGCATGGCCCAAGCAGCAGCCAACTGCCCAAGATCTTCCATGTCAACTGGTTCGGAAGGA  
CAAGGAAGGCAAATTCCTCTGGCCAGGCTTTGGAGAGAACTCCAGGGTGCTGGAGTGGATGTTCAACCGG  
ATCGATGGAAAAGCCAGCACCAACGTACGCCCATAGGCTACATCCCCAAGGAGGATGCCCTGAACCTGA  
20 AAGGCCTGGGGCACATCAACATGATGGAGCTTTTCAGCATCTCCAAGGAATTCTGGGACAAGGAGGTGGA  
AGACATCGAGAAGTATCTGGTGGATCAAGTCAATGCCGACCTCCCCTGTGAAATCGAGAGAGAGATCCTT  
GCCTTGAAGCAAAGAATAAGCCAGATGTAATCAGGGCCTGAGAATAAGCCAGATGTAATCAGGGCCTGAG  
TGCTTTACCTTTAAAATCATTAATAATAAATCCATAAGGTGCAGTAGGAGCAAGAGAGGGCAAGTGTTCC  
CAAATTGACGCCACCTAATAATCATCACACACCGGGAGCAGATCTGAAGGCACACTTTGATTTTTTTTAA  
25 GGATAAGAACCACAGAACACTGGGTAGTAGCTAATGAAATTGAGAAGGGAAATCTTAGCATGCCTCCAAA  
AATTCACATCCAATGCATACTTTGTTCAAATTTAAGGTTACTCAGGCATTGATCTTTTCAGTGTTTTTTC  
ACTTAGCTATGTGGATTAGCTAGAATGCACACCAAAAAGATACTTGAGCTGTATATATATATGTGTGTGT  
GTGTGTGTGTGTGTGTGTGTGTGCATGTATGTGCACATGTGTCTGTGTGATATTTGGTATGTGTATTTGT  
ATGTACTGTTATTCAAATAATATTTAATACCTTTGGAAAATCTTGGGCAAGATGACCTACTAGTTTTCTCT  
30 TGAAAAAAGTTGCTTTGTTATTAATATTGTGCTTAAATTATTTTTATACACCATTGTTTCCTTACCTTTA  
CATAATTGCAATATTTCCCCCTTACTACTTCTTGGAAAAAATTAGAAAATGAAGTTTATAGAAAAG  
(SEQ ID NO:6697)

35 gi|6679892|ref|NM\_008061.1| Mus musculus glucose-6-phosphatase, catalytic  
(G6pc), mRNA  
AGCAGAGGGATCGGGGCCAACCAGGGCTTGGACTCACTGCACGGGCTCTGCTGGCAGCTTCCTGAGGTACC  
AAGGGAGGAAGGATGGAGGAAGGAATGAACATTCTCCATGACTTTGGGATCCAGTCGACTCGCTATCTCC  
AAGTGAATTACCAAGACTCCCAGGACTGGTTCATCCTTGTGTCTGTGATTGCTGACCTGAGGAACGCCTT  
40 CTATGTCCTCTTTCCCATCTGGTTCATCTTAAAGAGACTGTGGGCATCAATCTCCTCTGGGTGGCAGTG  
GTCGGGAGACTGGTTCAACCTCGTCTTCAAGTGGATTCTGTTTGGACAACGCCCGTATTGGTGGGTCTGG  
ACACCGACTACTACAGCAACAGCTCCGTGCCTATAATAAAGCAGTTCCTGTACCTGTGAGACCGGACC  
AGGAAGTCCCTCTGGCCATGCCATGGGCGCAGCAGGTGTATACTATGTTATGGTCACTTCTACTCTTGCT  
ATCTTTTCGAGGAAAGAAAAAGCCAACGTATGGATTCCGGTGTGTTGAACGTCATCTTGTGGTTGGGATTCT  
45 GGGCTGTGCAGCTGAACGTCTGTCTGTCCCGGATCTACCTTGCTGCTCACTTTCCCCACCAGGTGCTGGC  
TGGAGTCTTGTGAGGCATTGCTGTGGCTGAAACTTTCAGCCACATCCGGGGCATCTACAATGCCAGCCTC  
CGGAAGTATTGTCTCATCACCATCTTCTTGTGTTTGGTTTCGCGCTTGGATTCTACCTGCTACTAAAAGGGC  
TAGGGGTGGACCTCCTGTGGACTTTGGAGAAAGCCAAGAGATGGTGTGAGCGGCCAGAATGGGTCCACCT  
TGACACTACACCTTTGCCAGCCTCTTCAAAAACCTGGGAACCTCTTGGGGTTGGGGCTGGCCCTCAAC  
50 TCCAGCATGTACCGGAAGAGCTGCAAGGGAGAACTCAGCAAGTCGTTCCCATTCGCTTCGCCTGCATTG  
TGGCTTCCTTGGTCTCCTGCATCTCTTTGACTCTCTGAAGCCCCCATCCCAGGTTGAGTTGATCTTCTA  
CATCTTGTCTTTCTGCAAGAGCGCAACAGTTCCTTTGCATCTGTGAGTCTTATCCCATACTGCCTAGCC  
CGGATCCTGGGACAGACACACAAGAAGTCTTTGTAAGGCATGCAGAGTCTTTGGTATTTAAAGTCAACCG  
CCATGCAAAGGACTAGGAACAATAAGCCTCTGAAACCCATTGTGAGGCCAGAGGTGTTGACATCGGCC  
55 CTGGTAGCCCTGTCTTTCTTTGCTATCTTAACCAAAAGGTGAATTTTTTACAAAGCTTACAGGGCTGTTTG

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CTTCTTGGGAAAAAAATTACAAAATAAA

(SEQ ID NO:6699)

**Example 6 siRNAs decrease mRNA levels *in vivo***

Male CMV-Luc mice (8-10 weeks old) from Xenogen (Cranbury, NJ) were administered cholesterol conjugated siRNA (see Table 16).

5                    Table 16. Solutions adminstered to mice

<u>Group</u>	<u>n</u>	<u>Injection Mix</u>
1	7	Buffer (PBS [pH 7.4])
2	8	Cholesterol conjugated siRNA (ALN-3001)

                    Table 17. Test iRNA agents targeting Luciferase

<u>siRNA</u>	<u>Sequence</u>
ALN-1070	5'-GAA CUG UGU GUG AGA GGU CCU-3' (SEQ ID NO:6700) 3'-CG CUU GAC ACA CAC UCU CCA GGA-5' (SEQ ID NO:6701)
ALN-1000	5'-GAA CUG UGU GUG AGA GGU CCU-GS-3' (SEQ ID NO:6702) 3'-CG CUU GAC ACA CAC UCU CCA GGA-5' (SEQ ID NO:6703)
ALN-3000	5'-GAA CUG UGU GUG AGA GGU CCU-3' (SEQ ID NO:6704) 3'-CS <sup>1</sup> GS <sup>1</sup> CUU GAC ACA CAC UCU CCA GGA-5' (SEQ ID NO:6705)
ALN-3001	5'-GAA CUG UGU GUG AGA GGU CCU-cho1. <sup>2</sup> -3' (SEQ ID NO:6706) 3'-CS <sup>1</sup> GS <sup>1</sup> CUU GAC ACA CAC UCU CCA GGA-5' (SEQ ID NO:6707)

10                    <sup>1</sup> 2' O-Me group is attached to the nucleotide and the nucleotides have phosphorothioate linkages (indicated by "s")

<sup>2</sup> cholesterol is conjugated to the antisense strand via the linker: U-pyrroline carrier-C(O)-(CH<sub>2</sub>)<sub>5</sub>-NHC(O)-cholesterol (via cholesterol C-3 hydroxyl).

15                    Animals were injected (tail vein) with a volume of 200-250 µl test solution containing buffer or an siRNA solution. Group 1 received buffer and group 2 received cholesterol conjugated siRNA (ALN-3001) at a dose of 50 mg/kg body weight. Twenty-two hours after injection, animals were sacrificed and livers collected. Organs were snap frozen on dry ice, then pulverized in a mortar and pestle.

20                    For Luciferase mRNA analysis (by the QuantiGene Assay (Genospectra, Inc.; Fremont, CA)), approximately 10 mg of tissue powder was resuspended in tissue lysis buffer, and processed according to the manufacturer's protocol. Samples of the lysate were hybridized with probes specific for Luciferase or GAPDH (designed using ProbeDesigner software (Genospectra, Inc., Fremont, CA) in triplicate, and processed for luminometric analysis. Values for Luciferase were normalized to GAPDH. Mean values were plotted with  
25                    error bars corresponding to the standard deviation of the Luciferase measurements.



Results indicated that the level of luciferase RNA in animals injected with cholesterol conjugated siRNA was reduced by about 70% as compared to animals injected with buffer (see FIGs 6A and 6b).

5           *In Vitro* Activity

HeLa cells expressing luciferase were transfected with each of the siRNAs listed in Table 17. ALN-1000 siRNAs were most effective at decreasing luciferase mRNA levels (~0.6 nM siRNA decreased mRNA levels to about ~65% the original expression level, and 1.0 nM siRNA decreased levels to about ~20% the original expression level); ALN-3001  
10 siRNAs were least effective (~0.6 nM siRNA had a negligible mRNA levels, and 1.0 nM siRNA decreased levels to about ~40% the original expression level).

Pharmacokinetics/Biodistribution

Pharmacokinetic analyses were performed in mice and rats. Test siRNA molecules  
15 were radioactively labeled with <sup>33</sup>P on the antisense strand by splint ligation. Labeled siRNAs (50mg/kg) were administered by tail vein injection, and plasma levels of siRNA were measured periodically over 24 hrs by scintillation counting. Cholesterol conjugated siRNA (ALN-3001) was discovered to circulate in mouse plasma for a longer period time than unconjugated siRNA (ALN-3000) (FIG. 7). RNase protection assays indicated that  
20 cholesterol-conjugated siRNA (ALN-3001) was detectable in mouse plasma 12 hours after injection, whereas unconjugated siRNA (ALN-3000) was not detectable in mouse plasma within two hours following injection. Similar results were observed in rats.

Mouse liver was harvested at varying time points (ranging from 0.08-24 hours) following injection with siRNA, and siRNA localized to the liver was quantified. Over the  
25 time period tested, the amount of cholesterol-conjugated siRNA (ALN-3001) detected in the liver ranged from 14.3-3.55 percent of the total dose administered to the mouse. The amount of unconjugated siRNA (ALN-3000) detected in the liver was lower, ranging from 3.91–1.75 percent of the total dose administered.

### Detection of siRNA in Different Tissues

Various tissues and organs (fat, heart, kidney, liver, and spleen) were harvested from two CMV-Luc mice 22 hours following injection with 50 mg/kg ALN-3001. The antisense strand of the siRNA was detected by RNase protection assay. The liver contained the greatest concentration of siRNA (~8-10 µg siRNA/g tissue); the spleen, heart and kidney contained lesser amounts of siRNA (~2-7 µg siRNA/g tissue); and fat tissue contained the least amount of siRNA (<~1 µg siRNA/g tissue).

### Glucose-6-phosphatase siRNA detection by RNase Protection Assay

Balbc mice were injected with U/U, 3'C/U, or 3' C/3' C siRNA (4 mg/kg) targeting glucose-6-phosphatase (G6Pase) (see Table 18). Administration was by hydrodynamic tail vein injection (hd) or non-hydrodynamic tail vein injection (iv), and siRNA was subsequently detected in the liver by RNase protection assay.

Table 18. Test iRNA agents targeting glucose-6-phosphatase

<b>siRNA</b>	<b>Description</b>
U/U	No cholesterol; dinucleotide 3' overhangs on sense and antisense strands
3'C/U	dinucleotide 3' overhangs on sense and antisense strands; cholesterol conjugated to 3' end of sense strand (mono-conjugate)
3'C/3'C	dinucleotide 3' overhangs on sense and antisense strands; cholesterol conjugated to 3' end of both sense and antisense strands (bis-conjugate)

Unconjugated siRNA (U/U) delivered by hd was detected by 15 min. post-injection (the earliest determined time-point) and was still detectable in the liver 18 hours post-injection.

Delivery by normal iv administration resulted in the greatest concentration of 3'C/3'C siRNA (the bis-cholesterol-conjugate) in the liver 1 hour post injection (as compared to the mono-cholesterol-conjugate 3'C/3'U siRNA). At 18 hours post injection, 3'C/3'C siRNAs and 3'C/U siRNA were still detectable in the liver with the bis-conjugate at higher levels compared to the mono-conjugate.

While this invention has been particularly shown and described with reference to preferred embodiments thereof, it will be understood by those skilled in the art that various

changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

**WHAT IS CLAIMED IS:**

1. An iRNA agent comprising a sense sequence and an antisense sequence, wherein  
5 the sense sequence has one or more asymmetrical 2'-O alkyl modifications and the antisense  
sequence has one or more asymmetrical phosphorothioate modifications, and the antisense  
sequence targets a human gene sequence.
2. The iRNA agent of claim 1, wherein at least one of said 2'-O-alkyl modifications  
10 is a 2'-OMe modification.
3. The iRNA agent of claim 1, wherein the sense sequence has at least 2  
asymmetrical 2'-O alkyl modifications.
- 15 4. The iRNA agent of claim 1, wherein the sense has at least 4 asymmetrical 2'-O  
alkyl modifications.
5. The iRNA agent of claim 4, wherein the asymmetrical modifications are 2'-OMe  
modifications.
- 20 6. The iRNA agent of claim 1, wherein the sense sequence has at least 6  
asymmetrical 2'-O alkyl modifications.
7. The iRNA agent of claim 6, wherein the asymmetrical modifications are 2'-OMe  
25 modifications.
8. The iRNA agent of claim 1, wherein the sense sequence has at least 8  
asymmetrical 2'-O alkyl modifications.
- 30 9. The iRNA agent of claim 8, wherein the asymmetrical modifications are 2'-OMe  
modifications.



10. The iRNA agent of claim 1, wherein all of the subunits of the sense sequence have an asymmetrical 2'-O alkyl modification.

5        11. The iRNA agent of claim 10, wherein the asymmetrical modifications are 2'-OMe modifications.

12. The iRNA agent of claim 1, wherein the antisense sequence has at least 2 asymmetrical phosphorothioate modifications.

10

13. The iRNA agent of claim 1, wherein the antisense sequence has at least 4 asymmetrical phosphorothioate modifications.

14. The iRNA agent of claim 1, wherein the antisense sequence has at least 6  
15 asymmetrical phosphorothioate modifications.

15. The iRNA agent of claim 1, wherein the antisense sequence has at least 8 asymmetrical phosphorothioate modifications.

20        16. The iRNA agent of claim 1, wherein all of the subunits of the sense sequence have an asymmetrical phosphorothioate modification.

17. The iRNA agent of claim 1, wherein the sense and antisense sequences are on different RNA strands.

25

18. The iRNA agent of claim 1, wherein the sense and antisense sequences are on the same RNA strand.

19. The iRNA agent of claim 1, wherein the sense and antisense sequences are fully  
30 complementary to each other.

20. The iRNA agent of claim 1, further comprising a cholesterol moiety.

21. The iRNA agent of claim 20, wherein said cholesterol moiety is coupled to a sense strand.

5

22. The iRNA agent of claim 20, further comprising a second cholesterol moiety.

23. The iRNA agent of claim 22, wherein said second cholesterol moiety is coupled to a sense strand.

10

24. The iRNA agent of claim 1, wherein said human gene is an oncogene.

25. The iRNA agent of claim 1, wherein said human gene is the apoB-100 gene.

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26. The iRNA agent of claim 1, wherein said human gene is the glucose-6-phosphatase gene.

27. The iRNA agent of claim 1, wherein the said human gene is the beta catenin gene.

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28. The iRNA agent of claim 1, wherein the iRNA agent is at least 21 nucleotides in length, and the duplex region of the iRNA is about 19 nucleotides in length.

29. The iRNA agent of claim 1, having a duplex region of about 19 subunits in length and one or two 3' overhangs of about 2 subunits in length.

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30. A pharmaceutical preparation comprising the iRNA agent of claim 1.

31. A method for reducing apoB-100 levels in a subject comprising administering to a subject an iRNA agent comprising a sense strand sequence and an antisense sequence, wherein the sense sequence has at least 4 asymmetrical 2'-O alkyl modifications and the

30

antisense sequence has at least 4 asymmetrical phosphorothioate modifications, and the antisense sequence targets apoB-100.

32. The method of claim 31, wherein the subject is suffering from a disorder  
5 characterized by elevated or otherwise unwanted expression of apoB-100, elevated or otherwise unwanted levels of cholesterol, and/or dysregulation of lipid metabolism.

33. The method of claim 32, wherein said disorder is chosen from the group of  
HDL/LDL cholesterol imbalance; dyslipidemias; hypercholesterolemia; statin-resistant  
10 hypercholesterolemia; coronary artery disease (CAD) coronary heart disease (CHD) atherosclerosis

34. A method for reducing glucose-6-phosphatase levels in a subject comprising  
administering to a subject an iRNA agent comprising a sense strand sequence and an  
15 antisense sequence, wherein the sense sequence has at least 4 asymmetrical 2'-O alkyl modifications and the antisense sequence has at least 4 asymmetrical phosphorothioate modifications, and the antisense sequence targets glucose-6-phosphatase.

35. The method of claim 34, wherein the iRNA agent is administered to a subject to  
20 inhibit hepatic glucose production, or for the treatment of a glucose-metabolism-related disorder.

36. The method of claim 35, wherein said disorder is diabetes.

25 37. The method of claim 35, wherein said disorder is type-2 diabetes.

38. A method of making an iRNA agent, the method comprising:  
providing a sense strand sequence having at least 4 asymmetrical 2'-O alkyl  
modifications and an antisense sequence having at least 4 asymmetrical phosphorothioate  
30 modifications, and allowing the sense and antisense strand to hybridize.

39. A method of stabilizing an iRNA agent, comprising selecting a sequence with activity, and introducing one or more asymmetrical modification in said sequence, wherein said modification decreases nuclease sensitivity while not decreasing activity.



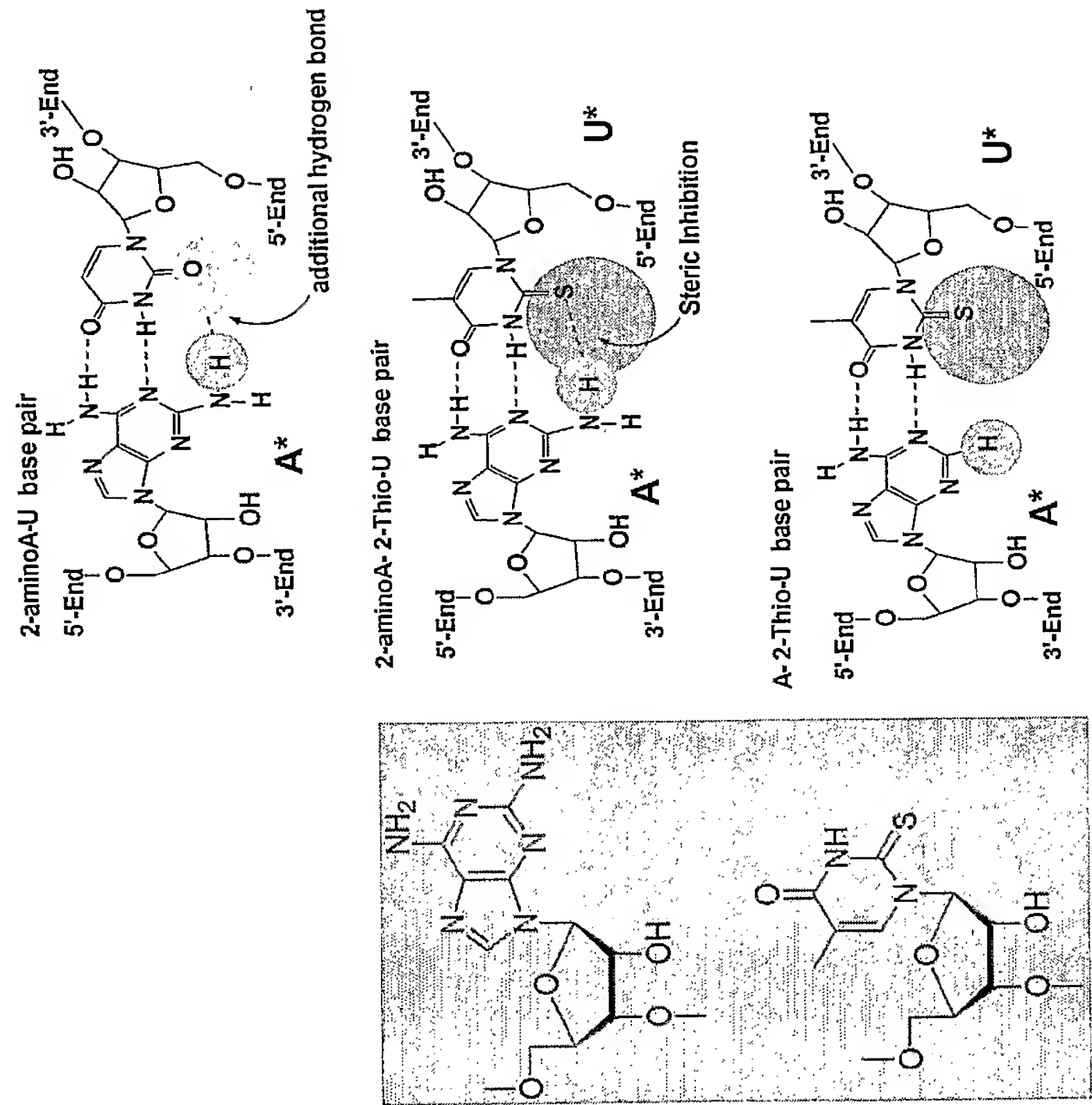


Figure 1

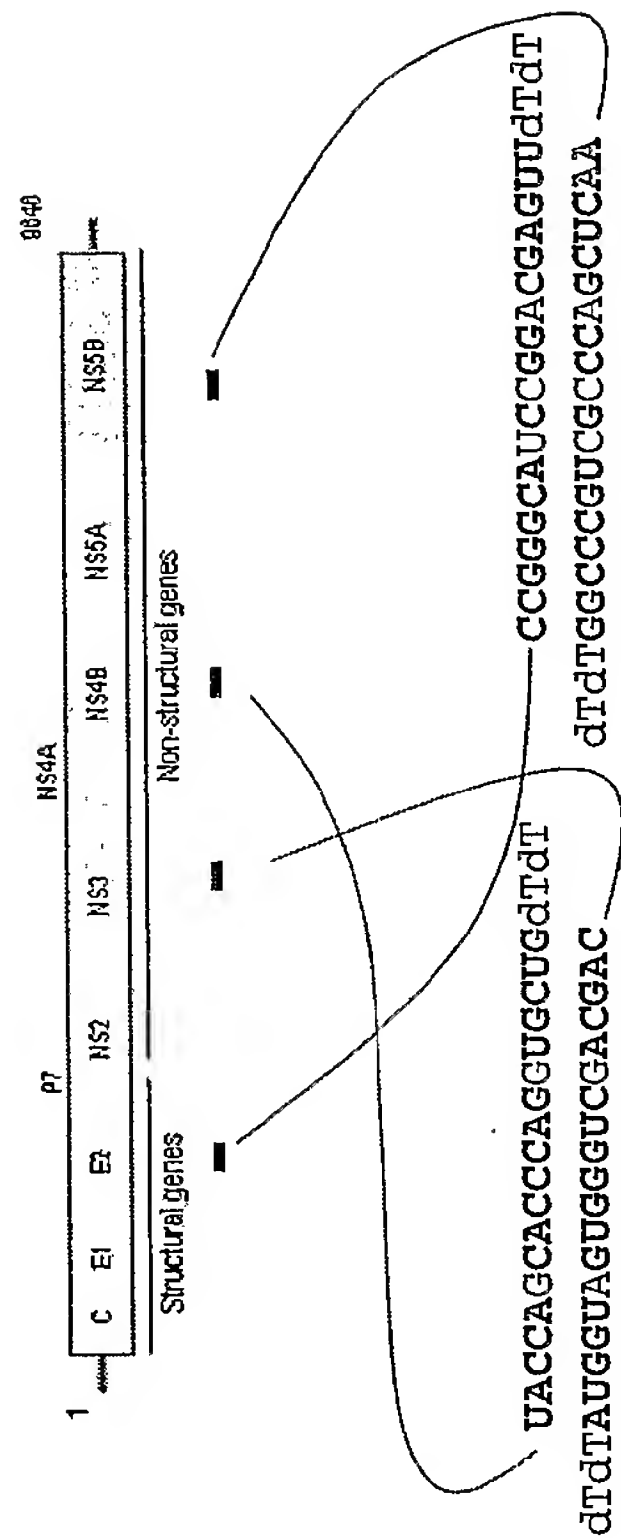


Figure 2

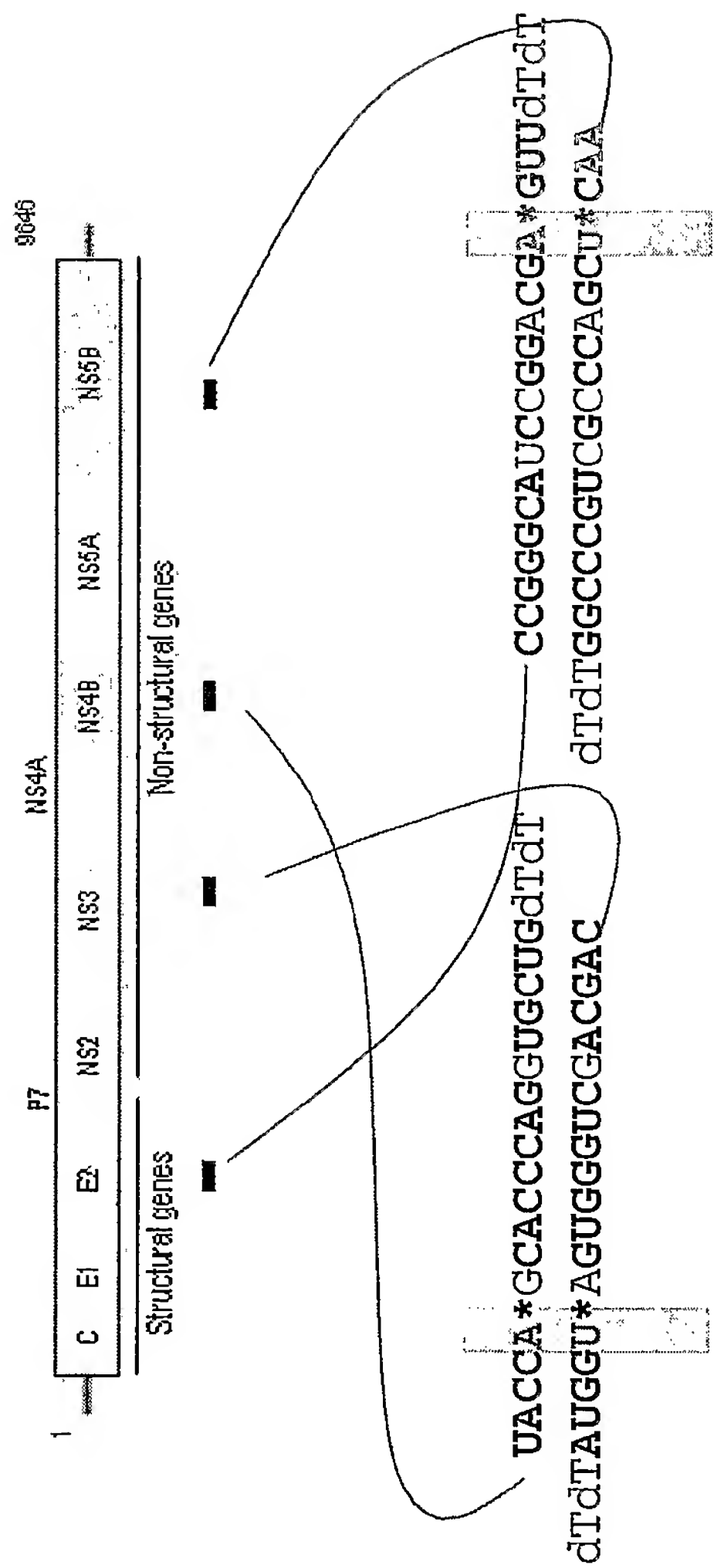


Figure 3

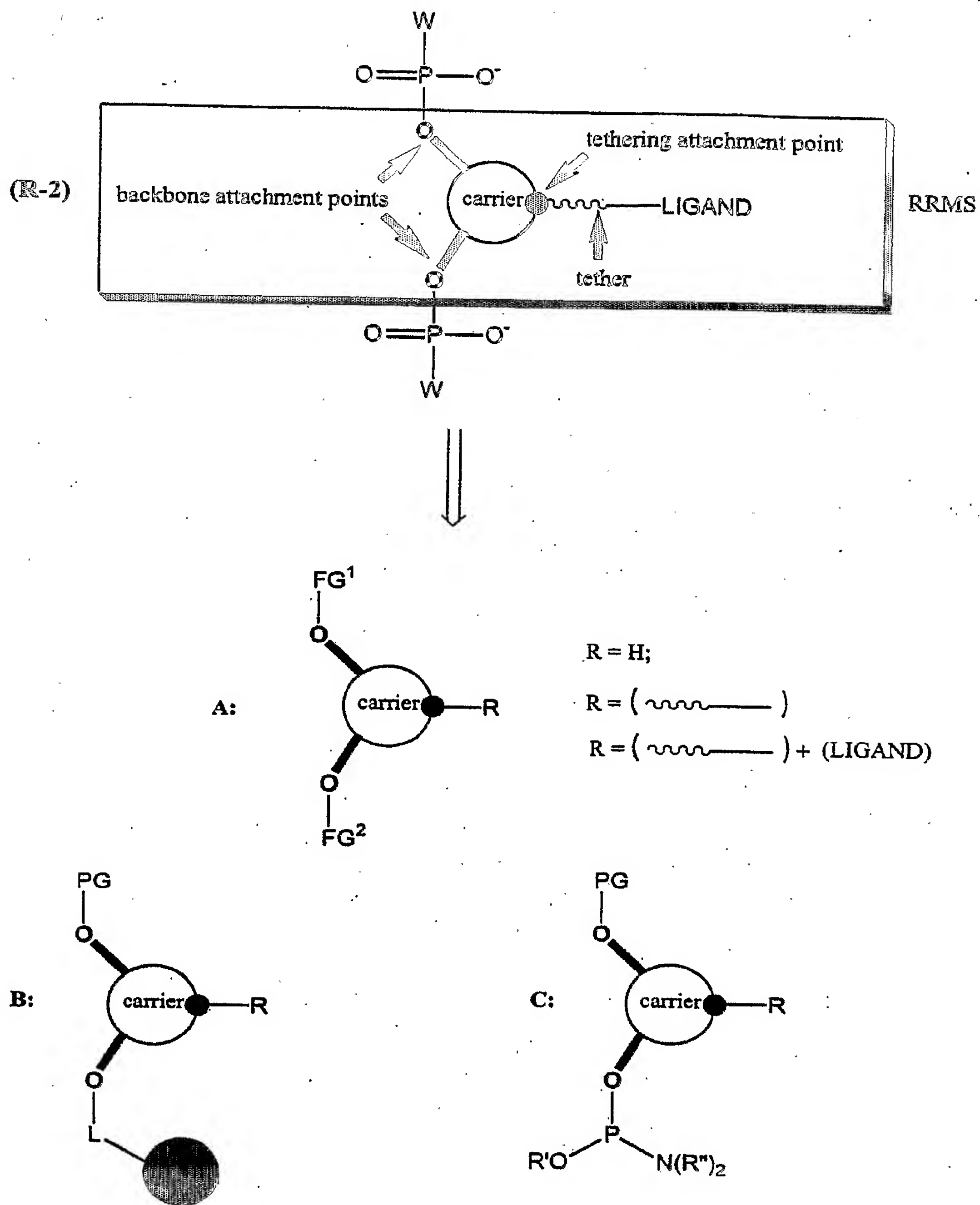


FIG. 4



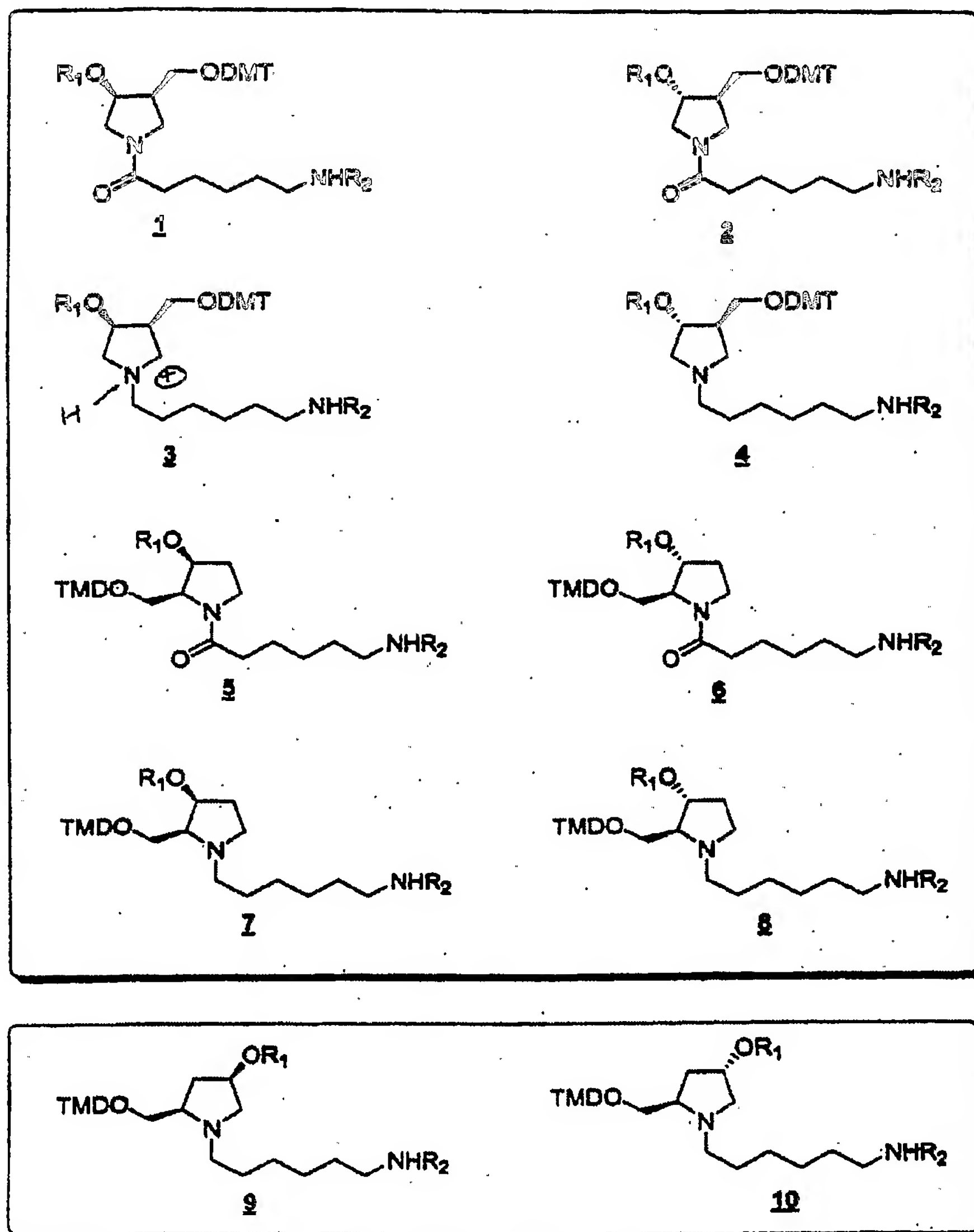


FIG. 5

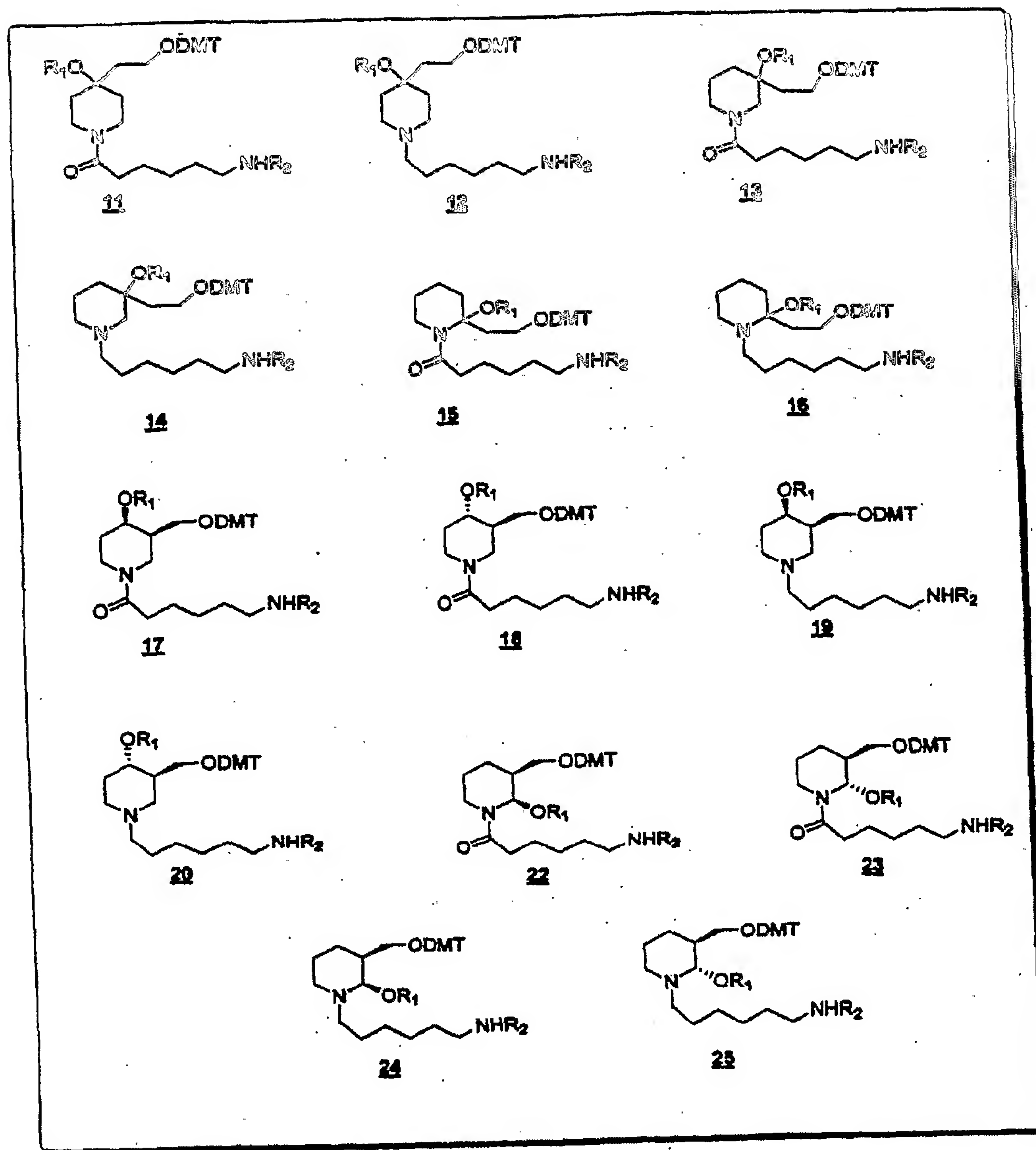


FIG. 5 (Cont'd)

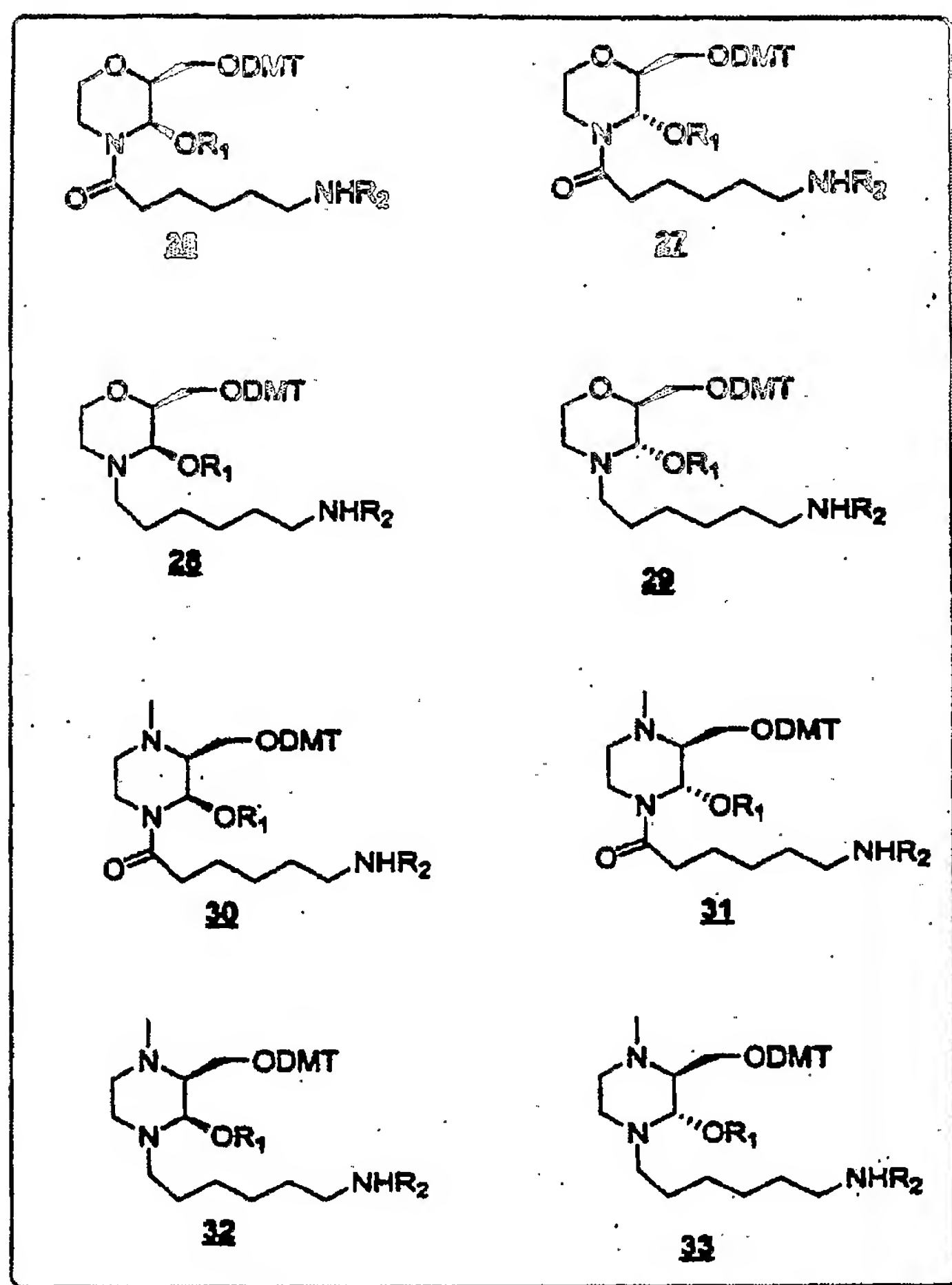


FIG. 5 (Cont'd)

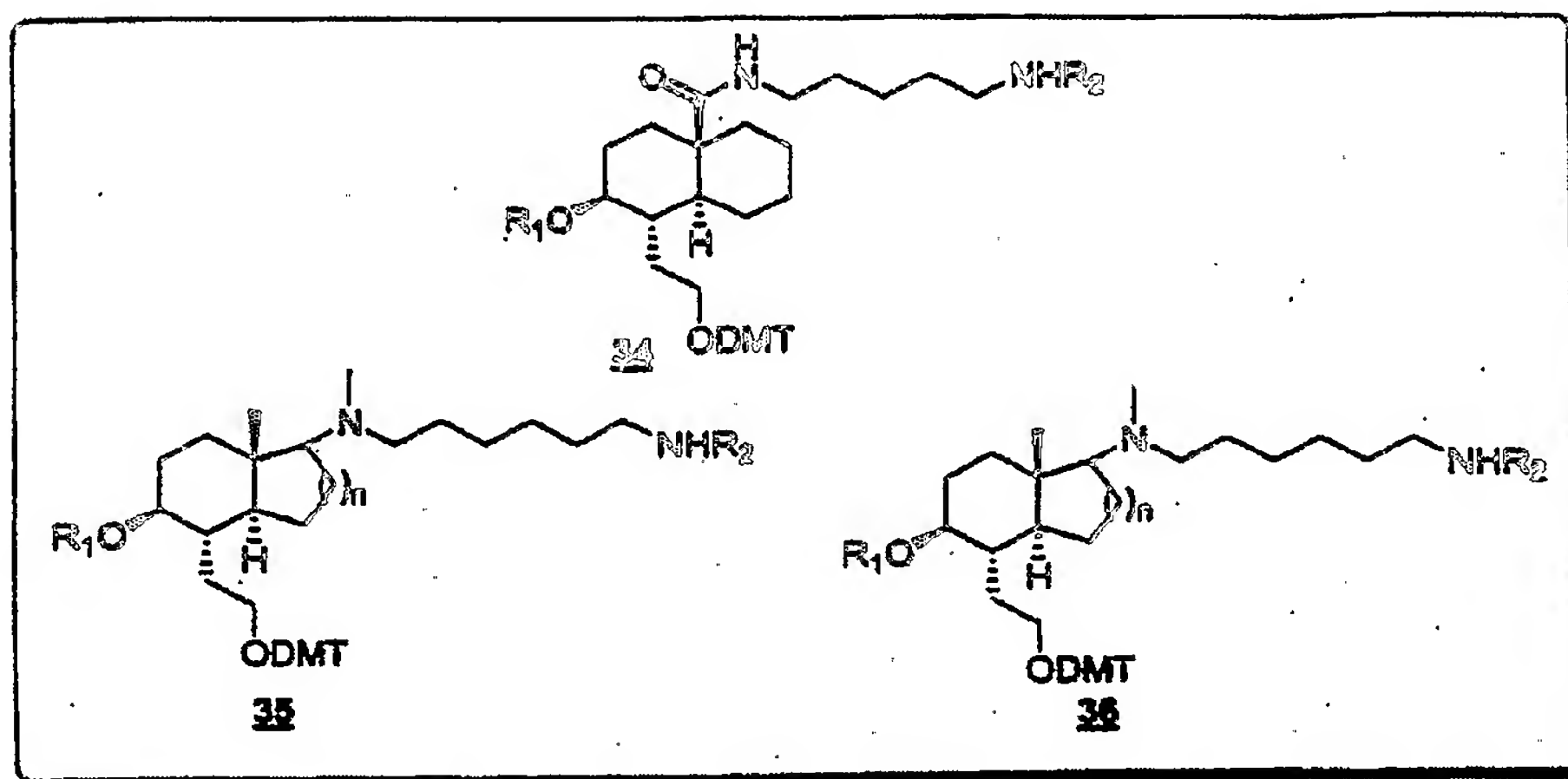


FIG. 5 (Cont'd)



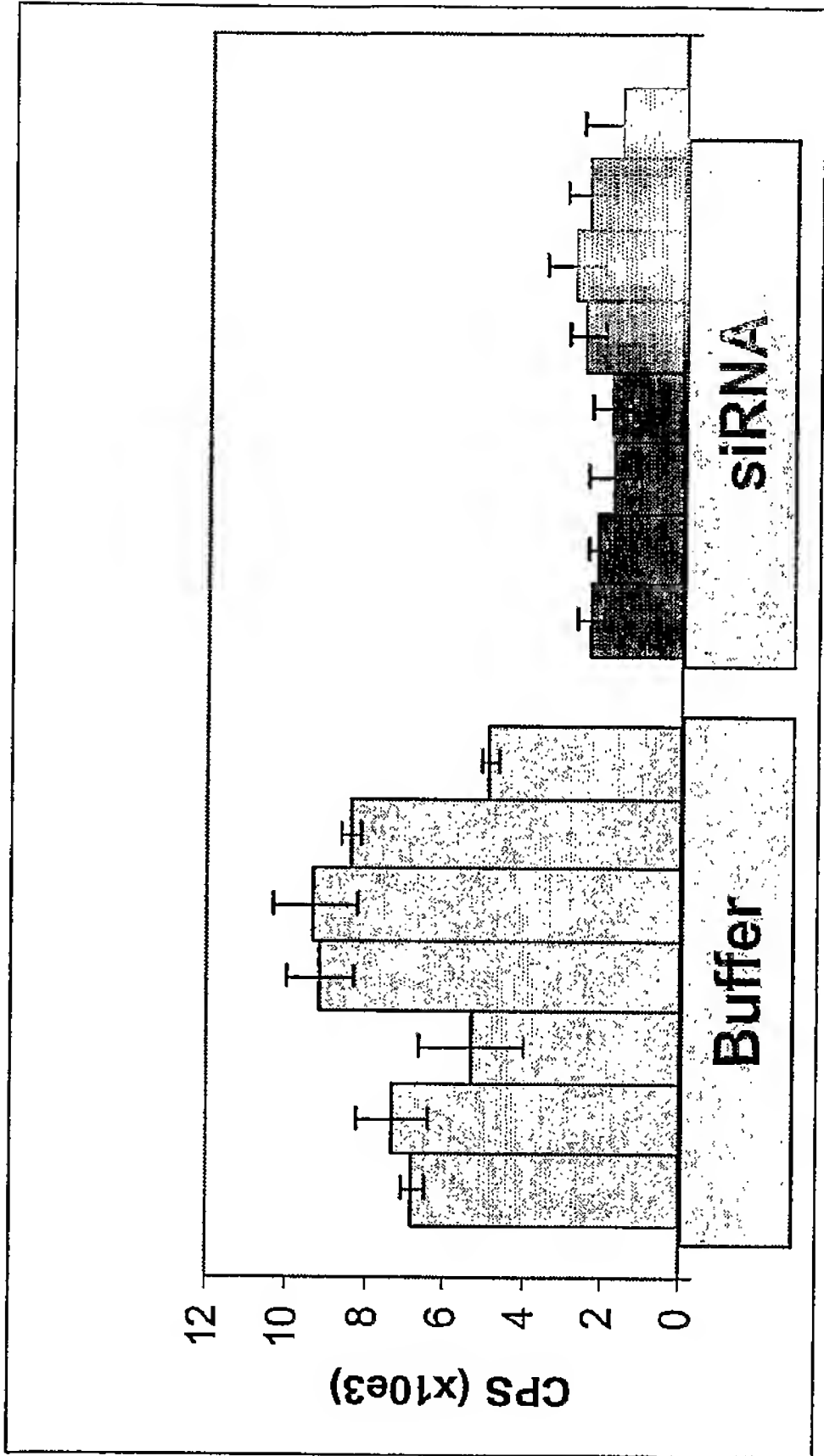


Figure 6A

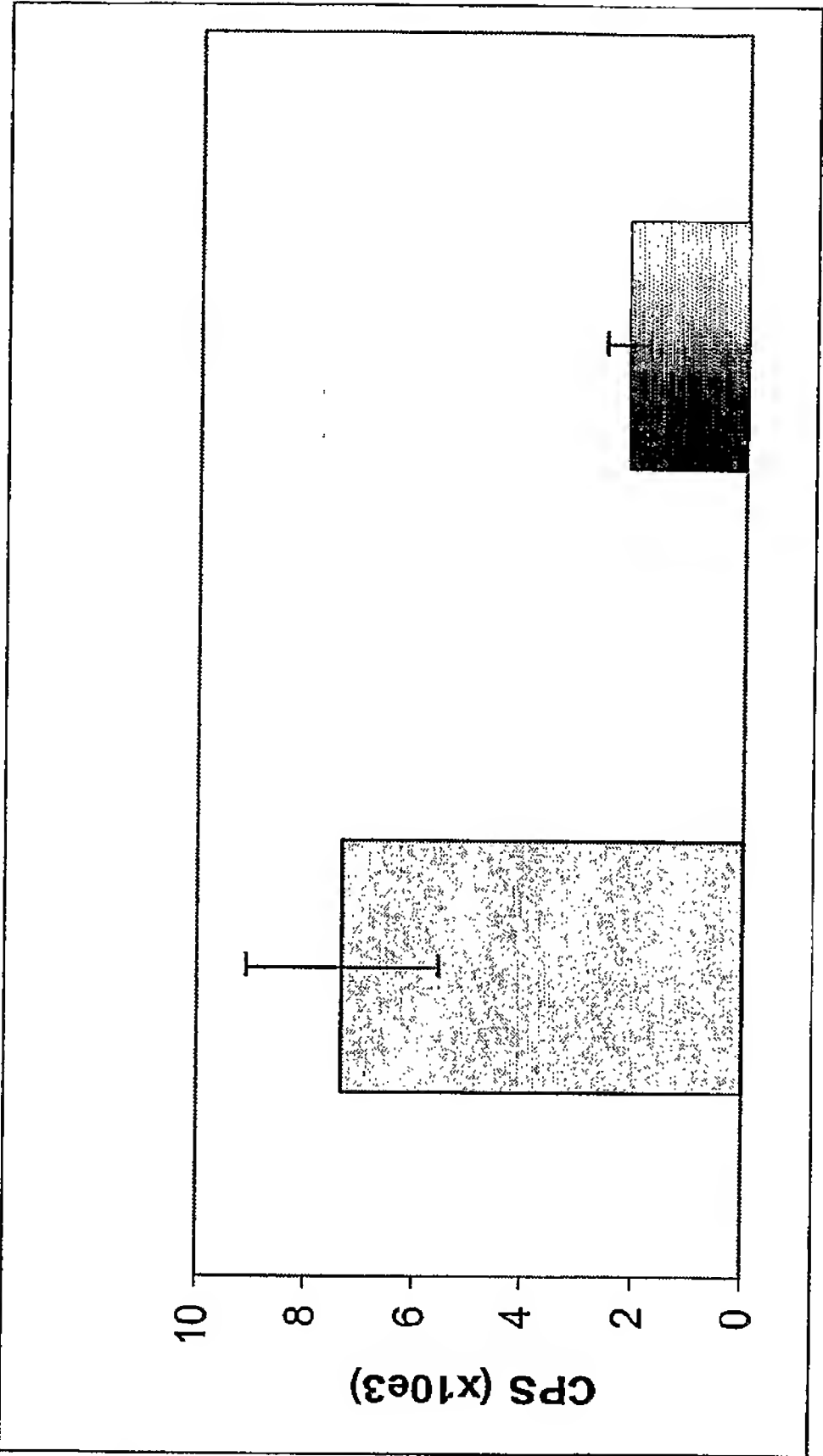


Figure 6B

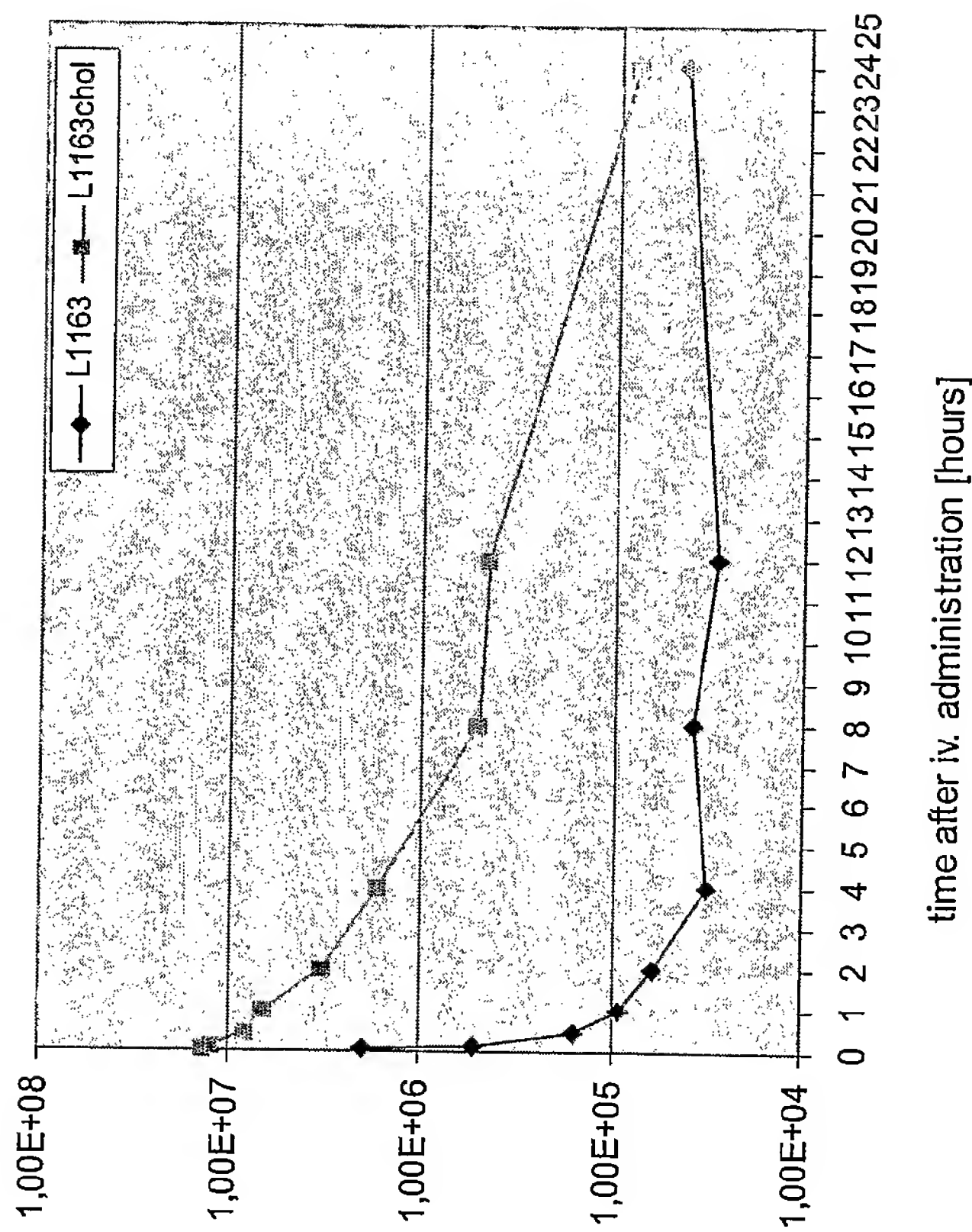


Figure 7